Cheminformatics in R

or *How to Start R and Never Have to Exit*

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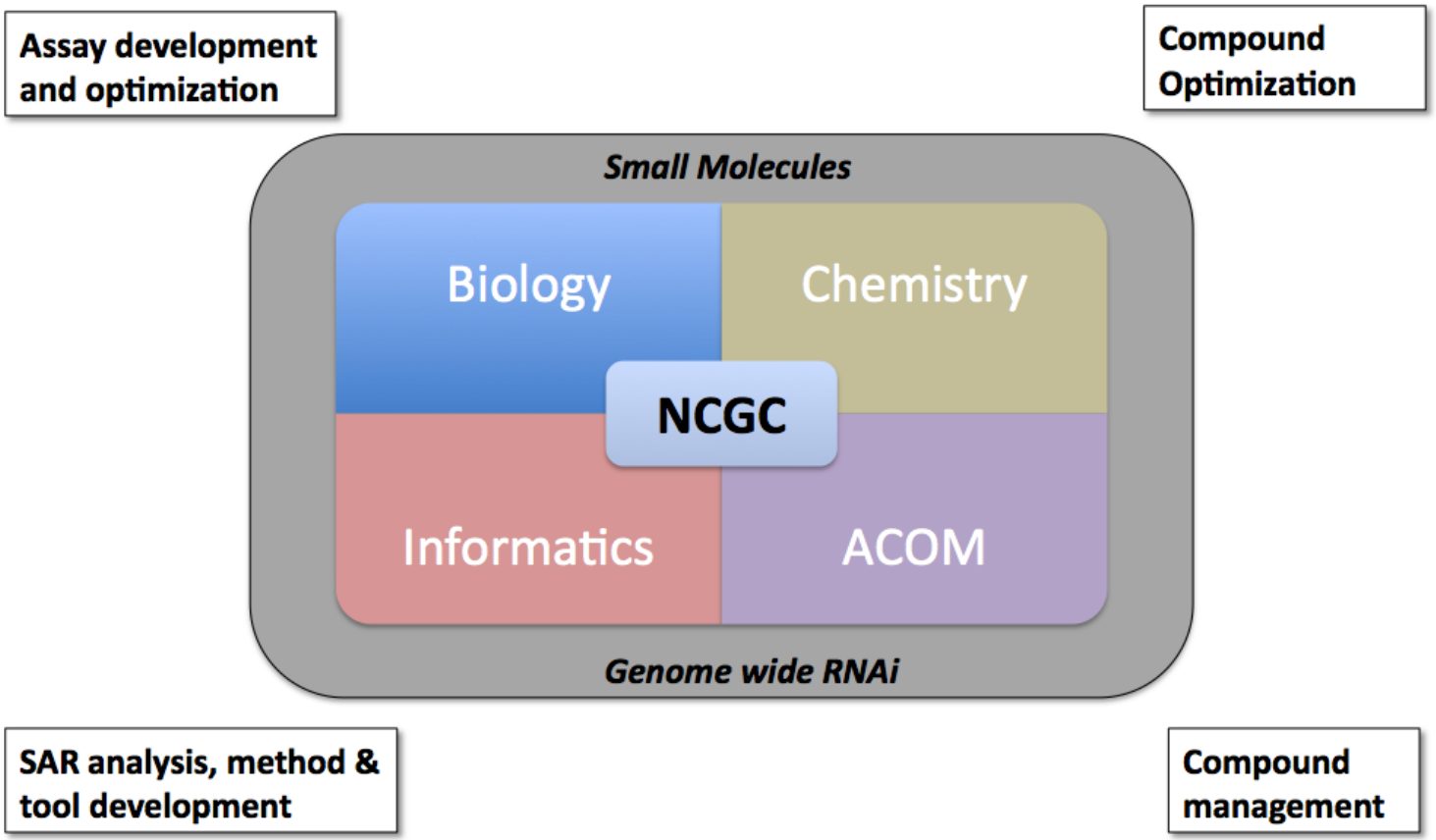
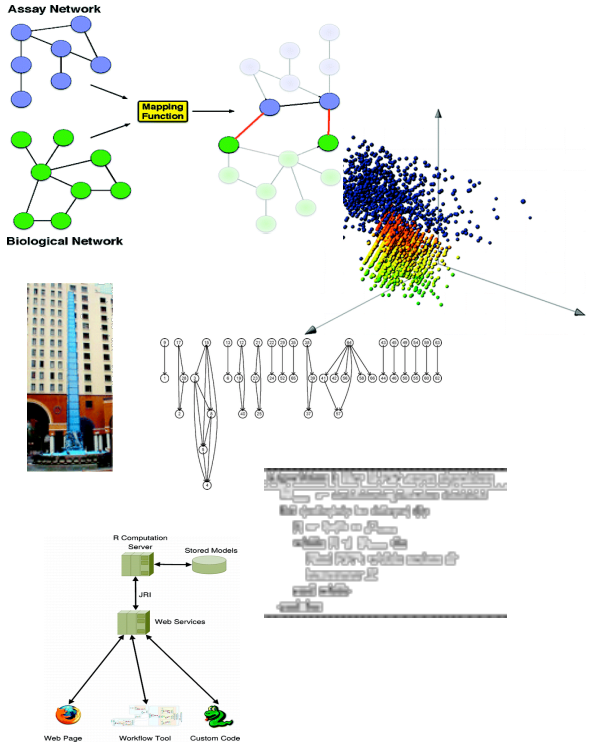
17th May, 2010
EBI, Hinxton

Background

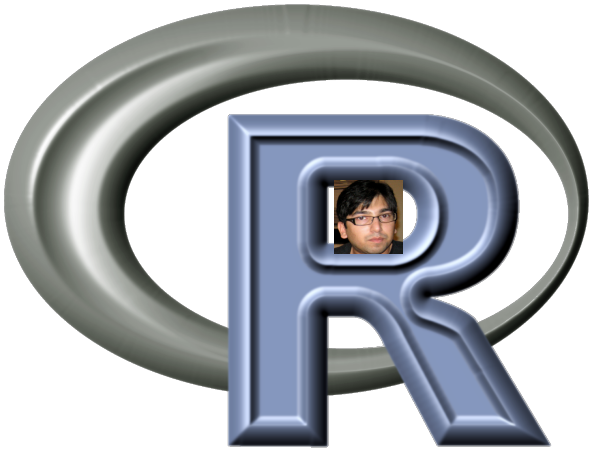

Assay development and optimization
Compound Optimization
Small Molecules
Biology
Chemistry
NCGC
Informatics
ACOM
Genome wide RNAi
SAR analysis, method & tool development
Compound management

Background

- Involved in various aspects of cheminformatics since 2002
  - QSAR modeling, virtual screening, polypharmacology, networks
  - Algorithm developement
  - Cheminformatics software development
- Core developer for the CDK



Background



- Pretty much live inside of R
- Been using it since 2003, developed a number of R packages, mostly public
- Make extensive use of R at NCGC for small molecule & RNAi screening

Acknowledgements

- `rcdk`
  - Miguel Rojas
  - Ranke Johannes
- CDK
  - Egon Willighagen
  - Christoph Steinbeck
  - ...

Resources

- Download binaries
  - If you're working on Unix it's a good idea to compile from source
- There's lots of documentation of varying quality
  - The R manual is a good document to start with
  - R Data Import and Export is **extremely** handy regarding data loading
  - A variety of short introductory tutorials as well as documents on specific topics in statistical modeling can be found here
- More general help can be obtained from
  - The R-help mailing list. Has a lot of renoowned experts on the list and if you can learn quite a bit of statistics in addition to getting R help just be reading the archives of the list. Note: they do expect that you have done your homework! See the posting guide
  - A useful reference for Python/Matlab users learning R

R Books

- A number of books are available ranging from introductions to R along with examples up to advanced statistical modeling using R.
- Data Analysis and Graphics Using R: An Example-based Approach by John Maindonald, John Braun
- Introductory Statistics with R by Peter Dalgaard
- Using R for Introductory Statistics by John Verzani
- If you end up programming a lot in R, you'll want to have Programming with Data: A Guide to the S Language by John M. Chambers

IDE's and editors

- Emacs + ESS - works on Linux, Windows, OS X. *Invaluable* if you are an Emacs user
- TINN-R is a small and useful editor for Windows
- You can also do R in Eclipse
  - StatET
  - Rsubmit
- A number of different GUI's are available for, which may be useful if you're an infrequent user
  - Rcommander
  - JGR
  - Rattle
  - PMG
  - SciViews-R
  - Red-R

What is R?

- R is an environment for modeling
  - Contains many prepackaged statistical and mathematical functions
  - No need to implement anything
- R is a matrix programming language that is good for statistical computing
  - Full fledged, interpreted language
  - Well integrated with statistical functionality
  - More details later

What is R?

- It is possible to use R just for modeling
- Avoids programming, preferably use a GUI
  - Load data → build model → plot data
- But you can also get much more creative
  - Scripts to process multiple data files
  - Ensemble modeling using different types of models
  - Implement brand new algorithms
- R is good for prototyping algorithms
  - Interpreted, so immediate results
  - Good support for vectorization
    - Faster than explicit loops
    - Analogous to `map` in Python and Lisp
  - Most times, interpreted R is fine, but you can easily integrate C code

What is R?

- R integrates with other languages
  - C code can be linked to R and C can also call R functions
  - Java code can be called from R and vice versa. See various packages at rosuda.org
  - Python can be used in R and vice versa using Rpy
- R has excellent support for publication quality graphics
- See R Graph Gallery for an idea of the graphing capabilities
- But graphing in R does have a learning curve
- A variety of graphs can be generated
  - 2D plots - scatter, bar, pie, box, violin, parallel coordinate
  - 3D plots - OpenGL support is available

Why Cheminformatics in R?

- In contrast to bioinformatics (cf. Bioconductor), not a whole lot of cheminformatics support for R
- For cheminformatics and chemistry relevant packages include
  - `rcdk`, `rpubchem`, `fingerprint`
  - `bio3d`, `ChemmineR`
- A lot of cheminformatics employs various forms of statistics and machine learning - R is exactly the environment for that
- We just need to add some chemistry capabilities to it

Outline

- An overview of the R language
- An overview of the CDK library
- Exploring the `rcdk` package
- Exploring the `rcdklibs` package
- Extending the code

Accessing packages

- From within R (you'll need 2.11.0 or better)

```
install.packages(c("rcdk","rpubchem"), dependencies = TRUE)
```

- Sources for `rcdk` and `rcdklibs` can be obtained from the Github repository
  - This is required if you want to modify Java code associated with `rcdk`
- Installable development packages (OS X, Linux, Windows) available from http://rguha.net/rcdk
  - These will make their way to CRAN

Workshop prerequisites

- Everything should be installed
- Running the code below should not give any errors

```
library(rcdk)
library(rpubchem)
source(helper.R)
```

- Most of the code snippets in these slides are contained in `code.R`
- You should have a `data/` directory containing various datasets used in this workshop
- You should have a `exercises/` directory containing the source code solutions to the exercises

Part I

Overview of R

Outline

The language

Parallel R

Database access

Working in R

- To get help for a function name do: `?functionname`
- If you don't know the name of the function, use: `help.search("blah")`
- R Site Search and Rseek are very helpful online resources
- To exit from the prompt do: `quit()`
- Two ways to run R code
  - Type or paste it at the prompt
  - Execute code from a source file: `source("mycode.R")`
- Saving your work
  - `save.image(file="mywork.Rda")` saves the whole workspace to *mywork.Rda*, which is a binary file
  - When you restart R, do: `load("mywork.Rda")` will restore your workspace
  - You can save individual (or multiple) objects using `save`

Basic types in R

Primitive types

- **numeric** - indicates an integer or floating point number
- **character** - an alphanumeric symbol (string)
- **logical** - boolean value. Possible values are TRUE and FALSE

Complex types

- **vector** - a 1D collection of objects of the same type
- **list** - a 1D container that can contain arbitrary objects. Each element can have a name associated with it
- **matrix** - a 2D data structure containing objects of the same type
- **data.frame** - a generalization of the matrix type. Each column can be of a different type

Primitive types

```
> x <- 1.2
> x <- 2

> y <- "abcdegf"
> y
[1] "abcdegf"

> z <- c(1,2,3,4,5)
> z
[1] 1 2 3 4 5

> z <- 1:5
> z
[1] 1 2 3 4 5
```

Matrices

- Make a matrix from a vector
- The matrix is constructed column-wise

```
> z <- c(1,2,3,4,5,6,7,8,9,10)
> m <- matrix(z, nrow=2, ncol=5)
> m
     [,1] [,2] [,3] [,4] [,5]
[1,]  1  3  5  7  9
[2,]  2  4  6  8  10
```

data.frame

- We want to store compound names and number of atoms and whether they are toxic or not
- Need to store: characters, numbers and boolean values

```
x <- c("aspirin", "potassium cyanide",
       "penicillin", "sodium hydroxide")
y <- c(21, 3, 41,3)
z <- c(FALSE, TRUE, FALSE, TRUE)
d <- data.frame(x,y,z)

> d
                x y z
1 aspirin 21 FALSE
2 potassium cyanide 3 TRUE
3 penicillin 41 FALSE
4 sodium hydroxide 3 TRUE
```

data.frame

- But do the column means? 6 months later, we probably won't know (easily)
- So we should add names

```
> names(d) <- c("Name", "NumAtom", "Toxic")
> d
              Name NumAtom Toxic
1 aspirin 21 FALSE
2 potassium cyanide 3 TRUE
3 penicillin 41 FALSE
4 sodium hydroxide 3 TRUE
```

- When adding column names, don't use the underscore character
- You can access a column of a `data.frame` by it's name: `d$Toxic`

Lists

- A 1D collection of arbitrary objects (`ArrayList` in Java)
- We can access the lists by indexing: `mylist[1]` or `mylist[[1]]` for the first element or `mylist[c(1,2,3)]` for the first 3 elements

```
x <- 1.0
y <- "hello there"
s <- c(1,2,3)
mylist <- list(x,y,s)

> mylist
[[1]]
[1] 1

[[2]]
[1] "hello there"

[[3]]
[1] 1 2 3
```

Lists

- It's useful to name individual elements of a list

```
x <- "oxygen"
z <- 8
m <- 32
mylist <- list(name="oxygen",
               atomicNumber=z,
               molWeight=m)
> mylist
$name
[1] "oxygen"

$atomicNumber
[1] 8

$molWeight
[1] 32
```

Lists

- We can then get the molecular weight by writing

```
> mylist$molWeight
[1] 32
```

Identifying types

- It's useful initially, to identify the type of the object
- Usually just printing it out explains what it is
- You can be more concise by doing

```
> x <- 1
> class(x)
[1] "numeric"

> x <- "hello world"
> class(x)
[1] "character"

> x <- matrix(c(1,2,3,4), nrow=2)
> class(x)
[1] "matrix"
```

Indexing

- Indexing fundamental to using R and is applicable to vectors, matrices, data.frame's and lists
- all indices start from 1 (not 0!)
- For a 1D vector, we get the i'th element by `x[i]`
- For a 2D matrix of data.frame we get the i, j element by `x[i,j]`
- But we can also index using vectors
  - Called an *index vector*
  - Allows us to select or exclude multiple elements simultaneously

Indexing

- Say we have a vector, `x` and a matrix `y`

```
> x
 [1] 1 2 3 4 5 6 7 8 9 10
> y
     [,1] [,2] [,3] [,4] [,5]
[1,]  1  4  7  10  13
[2,]  2  5  8  11  14
[3,]  3  6  9  12  15
```

- Some ways to get elements from `x`
- 5th element $\longrightarrow$ `x[5]`
- The 3rd, 4th and 5th elements $\longrightarrow$ `x[ c(3,4,5) ]`
- Everything **but** the 3rd, 4th and 5th elements $\longrightarrow$ `x[ -c(3,4,5) ]`

Indexing

- Say we have a matrix `y`

```
> y
     [,1] [,2] [,3] [,4] [,5]
[1,]  1  4  7  10  13
[2,]  2  5  8  11  14
[3,]  3  6  9  12  15
```

- Some ways to get elements from `y`
- Element in the first row, second column → `y[1,2]`
- All elements in the 1st column → `y[,1]`
- All elements in the 3rd row → `y[3,]`
- Elements in the first 2 columns → `y[ , c(1,2) ]`
- Elements **not** in the first 2 columns → `y[ , -c(1,2) ]`

Indexing

- You can also use a boolean vector to index another vector
- In this case, the index vector must of the same length as your target vector
- If the i'th element in the index vector is TRUE then the i'th element of the target is selected

```
> x <- c(1,2,3,4)
> idx <- c(TRUE, FALSE, FALSE, TRUE)
> x[ idx ]
[1] 1 4
```

- It's a pain to have to create a whole index vector by hand

Indexing

- A more intuitive way to do this, is to make use of R's vector operations
- `x == 2` will compare each element of `x` with the value 2 and return `TRUE` or `FALSE`
- The result is a boolean vector

```
> x <- c(1,2,3,4)
> x == 2
[1] FALSE TRUE FALSE FALSE
```

- So we can select the elements of x that are equal to 2 by doing

```
> x <- c(1,2,3,4)
> x[ x == 2 ]
[1] 2
```

Indexing

- Or select elements of x that are greater than 2

```
> x <- c(1,2,3,4)
> x[ x > 2 ]
[1] 3 4
```

- Or select elements of x that are 2 *or* 4

```
> x <- c(1,2,3,4)
> x[ x == 2 | x == 4 ]
[1] 2 4
```

- The single bar (|) is intentional
- Logical operations using vectors should use |, & rather than the usual ||, &&

List indexing

- With list objects we can index using `[` or `[[`
  - `[` keeps element names, `[[` drops names
- Can't use index vectors or boolean vectors with `[[`

```
> y <- list(a='b', b=123, x=c(1,2,3))
> y[3]
$x
[1] 1 2 3

> y[[3]]
[1] 1 2 3

> y[[1:2]]
Error in y[[1:2]] : subscript out of bounds
```

Subsetting

- Get a subset of the rows of a matrix or `data.frame` based on values in a certain column
- We can generate a boolean index vector
- For `data.frame`'s, we can use a more intuitive approach

```
d <- data.frame(a=1:10, b=runif(10), c=rnorm(10))

d[d$a <= 6,]

subset(d, a <= 6)
subset(d, a >= 7 & b < 0.4)
```

Merging data.frames

- Lets you join data.frames based on a common column
- Pretty much identical to an SQL join (and supports natural and outer joins)
- Very handy when merging data from multiple sources

```
d1 <- data.frame(mol=I(c("mol1", "mol2", "mol3")),
                 klass=c("active", "active", "inactive"))
d2 <- data.frame(molecule=I(c("mol1", "mol2", "mol3")),
                 TPSA=c(1.2,3.4,5.6), Kier1=c(5.7, 8.9, 12))

> merge(d1, d2, by.x="mol", by.y="molecule")
   mol klass TPSA Kier1
1 mol1 active 1.2 5.7
2 mol2 active 3.4 8.9
3 mol3 inactive 5.6 12.0
```

Functions in R

- Functions are much like in any other language
- R employs copy-on-write semantics
  - Send in a copy of an input variable if it will be modified in the function
  - Otherwise send in a reference
- Typing is dynamic

```
my.add <- function(x,y) {
  return(x+y)
}
```

- You can then call the function as `my.add(1,2)`
- In general, check for the type of object using `class()`
- Functions can be anonymous

Loop constructs

- R does not have C-style looping

```
for (i = 0; i < 10; i++) {
  print(i)
}
```

- Rather, it works like Python's for-in idiom

```
for (i in c(0,2,3,4,5,6,7,8,9)) {
  print(i)
}
```

Loop constructs

- In general, to loop n times, you create a vector with n elements, say by writing $1 : n$
- But like Python loops, you can just loop over elements of a vector or list and use them

```
> objects <- list(x=1, y="hello world", z=c(1,2,3))
> for (i in objects) print(i)
[1] 1
[1] "hello world"
[1] 1 2 3
```

- Good R style discourages explicit loops

Apply and friends

- Explicit loops (`for (...)`) are not idiomatic and can be slow
- `apply`, `lapply`, `sapply` resemble functional programming styles (but see `Reduce`, `Filter` and `Map` for alternatives)
- Good idea to master these forms

```
x <- c(1,2,3,4,5)
sapply(x, sqrt)
sapply(x, function(z) z+3)

sapply(x, function(z) rep(z,3), simplify=FALSE)
sapply(x, function(z) rep(z,3), simplify=TRUE)
```

- Handy for looping over vector elements

Looping over lists

- For list objects, use `lapply`
- The return value is a list - if it can be converted to a simple vector use `unlist` to do so

```
x <- list(x=1, b=2, c=3)

lapply(x, sqrt)
unlist(lapply(x, sqrt))

lapply(x, function(z) {
  return(z^2)
})
```

- The function argument of `lapply` should expect an object as the first argument
- Columns of a `data.frame` are lists, so `lapply` can be used to loop over columns

Looping over multiple objects

- What if you want to loop over two (or more) lists (or vectors) simulataneously
  - Like Pythons `zip` would allow
- Use `mapply` and provide a function that takes (at least) as many arguments as input vectors/lists

```
x <- 1:3
y <- list(a="Hello", b=12.34, c=c(1,2,3))
mapply(function(a,b) {
  print(a)
  print(b)
  print("---")
}, x, y)
```

Looping over matrices

- Use `apply` to operate on entire rows or columns of a matrix or `data.frame`
- Be careful when working on rows of a `data.frame` - behavior can be unexpected if all columns are not of the same type

```
m <- matrix(1:12, nrow=4)
apply(m, 1, sum) ## sum the rows
apply(m, 2, sum) ## sum the columns
```

- The function argument of `apply` should expect a vector as the first argument

Looping caveats

- The main thing to remember when using `apply`, `lapply` etc is nature of inputs to the user supplied function
- `apply` will send a vector (corresponding to a row or column)
- `lapply` and `sapply` will send a single element of the list/vector
- `mapply` will send a single element of each of the input lists/vectors
- The function argument of these methods can take anonymous functions or pre-defined functions

Loading data

- Writing vectors and matrices by hand is good for 15 minutes!
- Easier to read data from files
- R supports a variety of text and binary formats
- Certain packages can be loaded to handle special formats
  - Read from SPSS, Stata, SAS
  - Read microarray data, GIS data, chemical structure data
- Excel files can also be read (easiest on Windows)
- Data can be accessed from SQL databases (Postgres, MySQL, Oracle)

Reading CSV data

- Consider the extract of a CSV file below

```
ID,Class,Desc1,Desc2,Desc3,Desc4,Desc5
w150,nontoxic,0.37,0.44,0.86,0.44,0.77
c49,toxic,0.37,0.58,0.05,0.85,0.57
s97,toxic,0.66,0.63,0.93,0.69,0.08
```

- Key features include
  - A header line, naming the columns
  - An ID column and a Class column, both characters
- Reading this data file is as simple as

```
> dat <- read.csv("data1.csv", header=TRUE)
```

- If you print `dat` it will scroll down your screen

Reading CSV data

- To get a quick summary of the `data.frame` use the `str()` function

```
> str(dat)
'data.frame': 100 obs. of 7 variables:
 $ ID : Factor w/ 100 levels "a115","a180",..: 83 7 66 85 64 82 33 10 92 9
 $ Class: Factor w/ 2 levels "nontoxic","toxic": 1 2 2 1 2 1 1 1 1 2 ...
 $ Desc1: num 0.37 0.37 0.66 0.18 0.88 0.37 0.72 0.72 0.2 0.68 ...
 $ Desc2: num 0.44 0.58 0.63 0.09 0.1 0.14 0.03 0.15 0.65 0.66 ...
 $ Desc3: num 0.86 0.05 0.93 0.57 0.85 0.67 0.99 0.68 0.77 0.78 ...
 $ Desc4: num 0.44 0.85 0.69 0.85 0.58 0.17 0.95 0.19 0.69 0.61 ...
 $ Desc5: num 0.77 0.57 0.08 0.17 0.74 0.56 0.22 0.19 0.91 0.13 ...
```

What is a factor?

- The `factor` type is used to represent categorical variables
  - Toxic, non-toxic
  - Active, inactive
  - Yes, no, maybe
- They correspond to enum's in C/Java
- A factor variable looks like an ordinary vector of characters
- Internally they are represented by integers
- A factor variable has a property called the levels
  - Indicates what values are valid for the factor

```
> levels(dat$Class)
[1] "nontoxic" "toxic"
```

What is a factor?

- If you try to assign an invalid value to a factor you get a warning

```
> dat$Class[1] <- "Yes"
Warning message:
In `[<-.factor`(`*tmp*`, 1, value = "Yes") :
  invalid factor level, NAs generated

> dat$Class[1:10]
 [1] <NA> toxic toxic nontoxic toxic nontoxic nontoxic nontoxic
 [9] nontoxic toxic
Levels: nontoxic toxic
```

Operating on groups

- Factors are very useful when you'd like to operate on subsets of the data, as defined by factor levels
- Assay data might label molecules as active, inactive, inconclusive
- `by` is similar to `lapply` but operates on `data.frame`'s in a factor-wise way
- Takes a function argument which will receive a subset of the input `data.frame`, corresponding to a single level of the factor

```r
assay <- read.csv("data/aid2170.csv", header=TRUE)
str(assay)
levels(assay$PUBCHEM.ACTIVITY.OUTCOME)

## how many actives and inactives are there?
by(assay, assay$PUBCHEM.ACTIVITY.OUTCOME, function(x) {
  nrow(x)
})

## summary stats of the inhibiion values, by group
by(assay, assay$PUBCHEM.ACTIVITY.OUTCOME, function(x) {
  summary(x$Inhibition)
})

## or distributions of the inhibition values, by group
par(mfrow=c(1,2))
by(assay, assay$PUBCHEM.ACTIVITY.OUTCOME, function(x) {
  hist(x$Inhibition)
})
```

Outline

The language

Parallel R

Database access

Parallel R

- R itself is not multi-threaded
  - Well suited for embarassingly parallel problems
- Even then, a number of "large data" problems are not tractable
  - Recent developments on integrating R and Hadoop address this
  - See the `RHIPE` package
- We'll look at `snow` which allows distribution of processing on the same machine (multiple CPU's) or multiple machines
- But see `snowfall` for a nice set of wrappers around `snow`
- Also see `multicore` for a package that focuses on parallel processing on multicore CPU's

Trivial parallelization with `snow`

- `snow` lets you use multiple machines or multiple cores on a single machine
- Well suited for data-parallel problems
- If using multiple machines, data will be sent across the network, so large chunks of data can slow things down
- General strategy is
  - Initialize cluster
  - Send variables required for calculation to the nodes
  - Call a parallel function

Use case - exhaustive feature selection

- Given a set of N descriptors, find a n-descriptor subset that leads to a good predictive model
- Will obviously explode - ${}^{50}C_5 = 2,118,760$ descriptor combinations
- Usually we would employ a genetic algorithm or simulated annealing or even some form of stepwise selection
- For pedagogical purposes
  - how can we do this exhaustively?
  - how can we speed it up?

The data and a model

- Lets consider some melting point data
- Precalculated and reduced descriptor set
- 184 molecules in training set, 34 descriptors
- *Goal - find a good 4 descriptor OLS model*

[0]Bergstrom, C.A.S. et al, *J. Chem. Inf. Model.*, **2003**, 43, 1177–1185

A serial solution

- Evaluate all 4-member combinations of the numbers $\{1, 2, \ldots, 34\}$
  - These are the indices of the descriptor columns
- Loop over the rows, use the values as column indices of the descriptor matrix, build a model

```
## First some data prep
library(gtools)
load("data/bergstrom/bergstrom.Rda")

depv <- train.desc[,1]
desc <- train.desc[,-1]

idx <- 1:nrow(desc)
combos <- combinations(ncol(desc), 4)
```

A serial solution

```
rmse <- function(x,y) sqrt(sum((x-y)^2)/length(x))

system.time(
  rmse.serial <- apply(combos, 1, function(idx, mydata, y) {
    dat <- data.frame(y=y, x=mydata[,idx])
    m <- lm(y~., dat)
    return(rmse(m$fitted,y))
  }, mydata=desc, y=depv)
)
```

- Takes about 200 seconds

The parallel solution

- Code is pretty much identical
- First need to initialize the "cluster" - in this case we'll run multiple processes on the same machine

```
library(snow)
clus <- makeCluster(rep("localhost",2), type="SOCK")

system.time(
  rmse.par <- parApply(clus, combos, 1, function(idx, mydata, y) {
    dat <- data.frame(y=y, x=mydata[,idx])
    m <- lm(y~., dat)
    return(rmse(m$fitted,y))
  }, mydata=desc, y=depv)
)
```

- Takes about 120 seconds, but easily scales up with multiple cores

Outline

The language

Parallel R

Database access

R and databases

- Bindings to a variety of databases are available
  - Mainly RDBMS's but some NoSQL databases are being interfaced
- The R `DBI` spec lets you write code that is portable over databases
- Note that loading multiple database packages can lead to problems
- This can happen even when you don't explicitly load a database package
  - Some Bioconductor packages load the `RSQLite` package as a dependency, which can interfere with, say, `ROracle`

A quick look at RSQLite

- Not suitable for very large data or multiple connections
- Definitely look at sqldf, that makes it very easy to use SQL on R `data.frames`
- Very brief overview of what we can do with `RSQLite` for local storage
- Should transer easily to other databases

Basic usage - connecting

- We'll use a database I prepared and placed at `data/db/assay.db`
- Lets first get some information about the tables and field definitions

```
library(RSQLite)

## specific to RSQLite
sqlite <- dbDriver("SQLite")
con <- dbConnect(sqlite, dbname = "data/db/assay.db")

> dbListTables(con)
[1] "assay"

> dbListFields(con, "assay")
[1] "row_names" "aid" "PUBCHEM_SID" "PUBCHEM_CID"
  "PUBCHEM_ACTIVITY_OUTCOME" "PUBCHEM_ACTIVITY_SCORE"
  "PUBCHEM_ASSAYDATA_COMMENT"
```

Basic usage - querying

- The simplest way to get data is to slurp in the whole table as a `data.frame`
- Not a good idea if the table is very large

```
assay <- dbReadTable(con, "assay")

> str(assay)
'data.frame': 188264 obs. of 6 variables:
 $ aid : num 396 396 396 429 429 429 429 429 429 429 ...
 $ PUBCHEM_SID : int 10318951 10318962 10319004 842121 842122 842123 84212
 $ PUBCHEM_CID : int 6419748 5280343 969516 6603008 6602571 6602616 644371
 $ PUBCHEM_ACTIVITY_OUTCOME : chr "active" "active" "active" "inactive" ..
 $ PUBCHEM_ACTIVITY_SCORE : int 100 100 100 0 1 1 1 -3 0 0 ...
 $ PUBCHEM_ASSAYDATA_COMMENT: int 20061024 20060421 20061024 20061127 2006
```

Basic usage - querying

- Better to get subsets of the table via SQL queries
- Two ways to do it - get back all rows from the query or retrieve in chunks
- The latter is better when you might get a lot of rows

```
## query and get results in one go
dbGetQuery(con, "select distinct aid from assay")

## query and then get results in chunks
res <- dbSendQuery(con, "select * from assay where aid = 429")
fetch(res, n=10) ## get first 10 results
fetch(res, n=10) ## get next 10
fetch(res, n=-1) ## get remaining results

## no more rows to fetch
fetch(res, n=-1)

dbClearResult(res) ## a vital step!
```

Saving data in a database

- Can directly write a `data.frame` to a database file
- RSQLite will automatically generate a `CREATE TABLE` statement

```
library(rpubchem)

## get some assay data from PubChem
assay <- sapply(c(396, 429, 438, 445), function(x) {
  data.frame(aid=x, get.assay(x))[,1:6]
}, simplify=FALSE)

## join all assays into a single data.frame
assay <- do.call("rbind", assay)

## Make a new table
sqlite <- dbDriver("SQLite")
con <- dbConnect(sqlite, dbname = "assay.db")
dbWriteTable(con, "assay", assay)
dbDisconnect(con)
```

So why use a database?

- Dont have to load bulk CSV or .Rda files each time we start work
- Can index data in RDBMS's so queries can be very fast
- Good way to exchange data between applications (as opposed to .Rda files which are only useful between R users)
- All the code above, except for the `dbConnect` statement will be identical for PostgreSQL, MySQL etc.

Part II

The Chemistry Development Kit

Outline

Resources

- The CDK wiki
- The nightly build page
- Code snippets
- cdk-user mailing list
- Keyword list and feature list
- If you want to develop *with* the CDK, use the comprehensive jar file that contains all dependencies
  - from the nightly build page for the cutting edge
  - or from Sourceforge for the last stable release

Some CDK issues

- Learning the CDK is non-trivial
- No real tutorial but see here for a start
- Best place is to use the keyword list to find the relevant class and then look at the unit tests for a class

What does the CDK provide?

- Fundamental chemical objects
  - atoms
  - bonds
  - molecules
- More complex objects are also available
  - Sequences
  - Reactions
  - Collections of molecules
- Input/Output for a wide variety of molecular file formats
- Fingerprints and fragment generation
- Rigid alignments, pharmacophore searching
- Substructure searching, SMARTS support
- Molecular descriptors

Some design principles

- Abstraction is the key principle
  - Applies to chemical objects such as atoms, bonds
  - Also applied to input/output
- Rather than directly creating an atom object we use a factory method

```
IAtom atom = DefaultChemObjectBuilder.getInstance().
               newAtom();
```

and not

```
  IAtom atom = new Atom();
```

Some design principles

- By using `DefaultChemObjectBuilder` we don't worry how an atom or bond is created
- By using this type of abstraction we can load any file format without having to specify it
- Another aspect is the use of interfaces rather than concrete types
- A molecule is a collection of atoms and bonds
  - A graph view is not imposed directly
  - Molecular features such as aromaticity are properties of the atoms and bonds

Molecules

- A molecule is fundamentally represented as an IAtomContainer object
- For many purposes this is fine
- In some cases specialization is required so we have
  - Crystal
  - Ring
  - Fragment
- Some methods require a specific subclass
- Many methods simply require an IAtomContainer, so you can use any of the above subclasses

Molecules

- Similar procedure to getting an atom or bond object

```
IAtomContainer container = DefaultChemObjectBuilder.
                           getInstance().
                           newAtomContainer();
```

- Then we populate it

```
container.addAtom( atom1 );
container.addAtom( atom2 );
container.addBond( atom1, atom2, 1.5);
```

Outline

Introduction

I/O

Fingerprints

Substructures

Input/Output

- SMILES are a common format
- SMILES parsing, you will have to handle the `InvalidSmilesException`

```
SmilesParser sp = new SmilesParser(
                DefaultChemObjectBuilder.
                 getInstance());
IMolecule molecule = sp.parseSmiles("CCCC(CC)CC=CC=CC");
```

- Given a molecule object, we can create a SMILES

```
SmilesGenerator sg = new SmilesGenerator();
String smiles = sg.createSMILES(molecule);
System.out.println("SMILES = "+smiles);
```

Input/Output

- Reading files from disk is a common task
- A little more complex due to abstraction but is quite general

```
File file = new File("mols.sdf");
FileReader fileReader = new FileReader(file);
MDLV2000Reader reader = new MDLV2000Reader(fileReader);
IChemFile chemFile = (IChemFile) reader.
                     read(new ChemFile());
List containers = ChemFileManipulator.
                  getAllAtomContainers(chemFile);
```

Input/Output

- This is nice since it allows you to get all the molecules in the file at one go
- Not a good idea for very large SD files
- In such cases, use IteratingMDLReader
- Allows you to iterate over arbitrarily large SD files
- There is also an IteratingSMILESReader for big SMILES files

Input/Output

- Writing files is also supported for a wide variety of formats
- For example, to write to SD format

```
FileWriter w1 = new FileWriter(new File("molecule.sdf"));
try {
   MDLWriter mw = new MDLWriter(w1);
   mw.write(molecule);
   mw.close();
} catch (Exception e) {
   System.out.println(e.toString());
}
```

SD tags

- SD tags are a common way to associate property information with a molecular structure
- See PubChem SD files to get an idea of what we can put in them

```
  CDK 1/28/07,15:24

  2 1 0 0 0 0 0 0 0 0999 V2000
    0.0000 0.0000 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
    0.0000 0.0000 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
  1 2 1 0 0 0 0
M END
> <myProperty>
1.2

> <anotherProperty>
Hello world
```

SD tags

- When a molecule is read in from an SD file we can get the value of a given tag by doing

```
Object value = molecule.getProperty("myProperty");
```

- When writing a molecule we can supply a set of tags in a HashMap

```
HashMap tags = new HashMap();
tags.put("myProperty", new Double(1.2));
```

SD tags

- To ensure tags are written to disk we would do

```
FileWriter w1 = new FileWriter(new File("molecule.sdf"));
try {
   MDLWriter mw = new MDLWriter(w1);
   mw.setSdFields( tags );
   mw.write(molecule);
   mw.close();
} catch (Exception e) {
   System.out.println(e.toString());
}
```

SD tags

- A molecule might have several properties associated with it.
- We can avoid creating an extra HashMap, when writing them *all* to disk

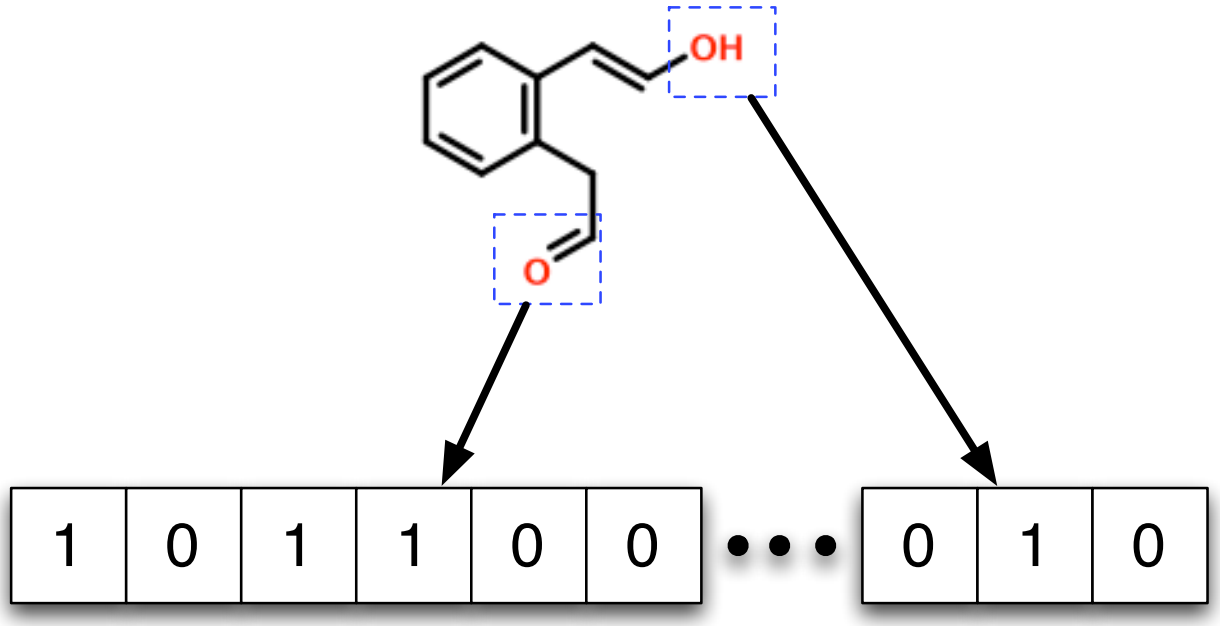
```
MDLWriter mw = new MDLWriter(w1);
mw.setSdFields( molecule.getProperties() );
mw.write(molecule);
mw.close();
```

Generating canonical SMILES

- The SmilesGenerator class will create canonical SMILES

```
String smiles = "C(C)(C)CC=CC(C(CC(C))CC)CC";
SmilesParser sp = new SmilesParser();
IMolecule mol = sp.parseSmiles(smiles);

SmilesGenerator sg = new SmilesGenerator();
String canSmi = sg.createSMILES(mol);
```

Fingerprints



- Used in many areas - database screening, diversity analysis, modeling

Outline

Fingerprints

- The simplest fingerprint looks for specific substructures and sets a specific bit
  - MACCSFingerprinter
  - SubstructureFingerprinter
- Hashed fingerprints don't maintain a correspondence between bit position and substructural feature

Getting fingerprints

- The CDK can generate binary fingerprints
- This gives a default fingerprint of 1024 bits - but you can specify smaller or larger fingerprints
- The CDK also provides variants of the default fingerprint
  - MACCSFingerprint
  - ExtendedFingerPrinter - includes bits related to rings
  - GraphOnlyFingerprinter - simplified version of fingerprinter that ignores bond order
  - SubstructureFingerprinter - generates fingerprints based on a specified set of substructures

```
IFingerprinter fprinter = new Fingerprinter()

BitSet fingerprint = fprinter.getFingerprint(molecule);
```

Evaluating similarity

- Given two molecules we are interested in determining how similar they are
- A common approach is to evaluate their fingerprints
- Calculate a similarity metric (e.g., Tanimoto coefficient)

```
BitSet fp1 = Fingerprinter.getFingerprint(molecule1);
BitSet fp2 = Fingerprinter.getFingerprint(molecule2);

float tc = Tanimoto.calculate(fp1, fp2);
```

Outline

Substructure searching

- Identify the presence/absence of a substructure in a molecule

```
IAtomContainer mol = ...;

SMARTSQueryTool sqt = new SMARTSQueryTool("C");
sqt.setSmarts("C(=O)C");
boolean matched = sqt.matches(mol);
```

- In many cases we're interested in all the possible matches

```
List<List<Integer>> maps;
maps = sqt.getUniqueMatchingAtoms();
```

- `maps.size()` gives you the number of matches
- Each element of `maps` is a sequence of atom ID's

Pharmacophores

- We'll look at constructing a pharmacophore query by hand
- Generally, you'd read it from a file
- Given a query we can search for that in a target molecule
- The target molecule should have 3D coordinates
- Generally you'll examine multiple conformers for a given molecule

Pharmacophores

- Construct pharmacophore groups

```
PharmacophoreQueryAtom o =
   new PharmacophoreQueryAtom("D", "[!H0;#7,#8,#9]");
PharmacophoreQueryAtom n1 =
   new PharmacophoreQueryAtom("A", "c1ccccc1");
PharmacophoreQueryAtom n2 =
   new PharmacophoreQueryAtom("A", "c1ccccc1");
```

Pharmacophores

- Construct pharmacophore constraints

```
PharmacophoreQueryBond b1 =
  new PharmacophoreQueryBond(o, n1, 4.0, 4.5);
PharmacophoreQueryBond b2 =
   new PharmacophoreQueryBond(o, n2, 4.0, 5.0);
PharmacophoreQueryBond b3 =
   new PharmacophoreQueryBond(n1, n2, 5.4, 5.8);
```

Pharmacophores

- Given pharmacophore groups and constraints, we construct a pharmacophore query
- Design to have the same semantics as a normal molecule

```
QueryAtomContainer query =
    new QueryAtomContainer();

query.addAtom(o);
query.addAtom(n1);
query.addAtom(n2);

query.addBond(b1);
query.addBond(b2);
query.addBond(b3);
```

Pharmacophores

- Given the query we can now perform a pharmacophore search

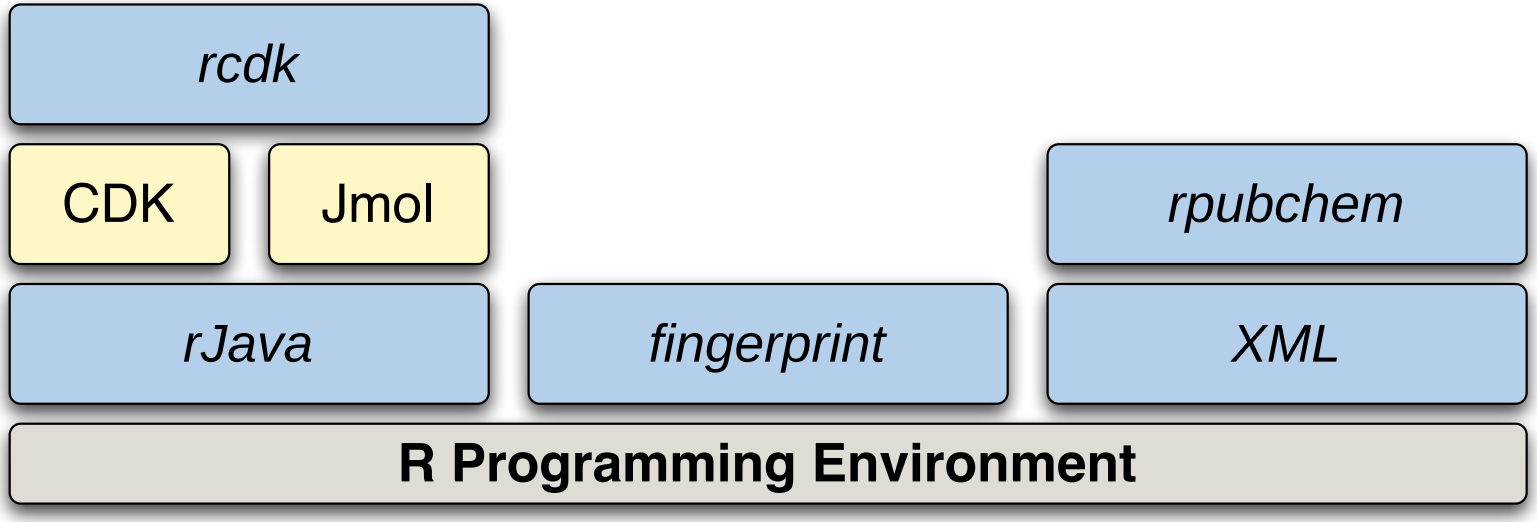
```
IAtomContainer aMolecule;

// load in the molecule

PharmacophoreMatcher matcher =
    new PharmacophoreMatcher(query);
boolean status = matcher.matches(aMolecule);
if (status) {
  // get the matching pharmacophore groups
  List<List<PharmacophoreAtom>> pmatches =
     matcher.getUniqueMatchingPharmacophoreAtoms();
}
```

Part III

Cheminformatics & R - `rcdk`

Using the CDK in R

- Based on the `rJava` package
- Two R packages to install (not counting the dependencies)
- Provides access to a variety of CDK classes and methods
- Idiomatic R



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Reading in data

- The CDK supports a variety of file formats
- `rcdk` loads all recognized formats, automatically
- Data can be local or remote

```
mols <- load.molecules( c("data/io/set1.sdf",
                          "data/io/set2.smi",
                          "http://rguha.net/rcdk/remote.sdf"))
```

- Gives you a `list` of Java references representing `IAtomContainer` objects
- Can't do much with these objects, except via `rcdk` functions

Reading structures from text files

- SMILES strings can be contained in arbitrary text files (such as CSV)
- If you read such a file with `read.table` or `read.csv`, make sure to set `comment.char=""`
- Also a good idea to specify the `colClasses` argument or else `as.is=TRUE`- otherwise SMILES will be read in as factors

Reading SMILES strings

- Also useful to load molecules directly from a SMILES string
- `parse.smiles` parses a single molecule

```
mol <- parse.smiles("c1ccccc1C(=O)N")

## loop over multiple SMILES
smiles <- c("CCC", "c1ccccc1",
            "C(C)(C=O)C(CCNC)C1CC1C(=O)")
mols <- sapply(smiles, parse.smiles)
```

- But the second call is inefficient, especially for large SMILES collections

Efficient SMILES parsing

- By default *parse.smiles* instantiates a SMILES parser object (`SmilesParser`)
- So when looping over a vector of SMILES strings we're creating a parser object each time
- In such a case, specify a parser object explicitly - 2X speedup

```
smilesParser <- get.smiles.parser()

## now specify this parser
smiles <- c("CCC","c1ccccc1","C(C)(C=O)C(CCNC)C1CC1C(=O)")
mols <- sapply(smiles, parse.smiles, parser = smilesParser)
```

Efficient SMILES parsing


```
> parser <- get.smiles.parser()
> smiles <- rep(c("CCC",
                  "c1ccccc1",
                  "C(C)(C=O)C(CCNC)C1CC1C(=O)"),
                 500)

> system.time(junk <- sapply(smiles, parse.smiles))
   user system elapsed
  4.088 0.106 3.946

> system.time(junk <- sapply(smiles, parse.smiles, parser=parser))
   user system elapsed
  1.792 0.032 1.705
```

You get what is provided . . . and no more

- CDK philosophy is not to do extra work
- For file reading this implies that it only parses what is specified in the file and will not perform operations that are not explicitly indicated
- As a result some features (isotopic masses) of molecules and atoms are not automatically configured
- `load.molecule` **will do these extra steps**
- `parse.smiles` **will not**

Configuring molecules


```
## no explicit configuration needed
mols <- load.molecules("data/io/bp.smi")
get.exact.mass(mols[[1]])

## explicit configuration required
mol <- parse.smiles("c1ccccc1")
get.exact.mass(mol)
```

- The last call will give a `NullPointerException` since the isotopic masses have not been configured

Configuring molecules

- When parsing SMILES, do the configuration by hand

```
smi <- "OC(=O)C1=C(C=CC=C1)OC(=O)C"
mol <- parse.smiles(smi)

## do the configuration
do.typing(mol) ## not required in recent versions
do.aromaticity(mol) ## not required in recent versions
do.isotopes(mol)

## now, this works
get.exact.mass(mol)
```

Hydrogens - implicit & explicit

- SMILES indicates that when hydrogens are not specified, they are to be considered implicit
- But MDL MOL files have no such specification, so if no H's specified, the molecule will not have explicit or implicit hydrogens

```
mol <- load.molecules("data/noh.mol")[[1]]
unlist(lapply(get.atoms(mol), get.symbol))
```

- In such cases, `convert.implicit.to.explicit` will add implicit H's (to satisfy valencies) and then convert them to explicit

```
convert.implicit.to.explicit(mol)
unlist(lapply(get.atoms(mol), get.symbol))
```

A note on function calls

- R uses copy-on-write semantics for function calls
  - If a function modifies its input argument, R will send a copy of the input variable to the function
  - Otherwise send a reference
  - "Safety" of call-by-value, efficiency of call-by-reference
- In contrast, `convert.implicit.to.explicit` modifies the input argument
  - No return value
- In general `rJava` allows you to work with Java objects using call-by-reference semantics

Writing molecules

- Currently only SDF is supported as an output file format
- By default a multi-molecule SDF will be written
- Properties are not written out as SD tags by default

```
smis <- c("c1ccccc1", "CC(C=O)NCC", "CCCC")
mols <- sapply(smis, parse.smiles)

## all molecules in a single file
write.molecules(mols, filename="mols.sdf")

## ensure molecule data is written out
write.molecules(mols, filename="mols.sdf", write.props=TRUE)

## molecules in individual files
write.molecules(mols, filename="mols.sdf", together=FALSE)
```

Generating SMILES

- Finally, we can also create SMILES strings from molecules via `get.smiles`
- Works on a single molecule at a time
- Canonical SMILES are generated by default

```
smis <- c("c1ccccc1", "CC(C=O)NCC", "CCCC")
mols <- sapply(smis, parse.smiles)

lapply(mols, get.smiles)
```

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Accessing attached data

- Some file formats allow you to attach data to a structure
- SDF is a good example, using named tags and associated values
- For example, a DrugBank SDF has fields such as

```
> <DRUGBANK_ID>
DB00135

> <DRUGBANK_GENERIC_NAME>
L-Tyrosine

> <DRUGBANK_MOLECULAR_FORMULA>
C9H11NO3

> <DRUGBANK_MOLECULAR_WEIGHT>
181.1885
```

Accessing data fields

- The CDK reads SDF tags and their values into the `IAtomContainer` object
- We can access them via the `get.property` and `get.properties`

```
> mols <- load.molecules("data/io/set1.sdf")
> get.properties(mols[[1]])
$DRUGBANK_ID
[1] "DB00135"

$DRUGBANK_IUPAC_NAME
[1] "(2S)-2-amino-3-(4-hydroxyphenyl)propanoic acid"

$`cdk:Title`
[1] "135"

...
```

Accessing data fields

- If you know the name of the field, just pull the value directly

```
get.property(mols[[1]], "DRUGBANK_GENERIC_NAME")
```

- Note that values for **all** tags are `character`, so you need to cast them to the appropriate types manually

Extra tags

- In some cases, you'll see tag names that are not in the SDF file
- The CDK uses molecule property fields to attach arbitrary data.
- For example, the title field from a SDF entry is stored using the `cdk:Title` name
- In general, all CDK-derived properties have names prefixed by "`cdk:`"

```
## identify CDK-derived properties
props <- get.properties(mols[[1]])
props[ grep("^cdk:", names(props)) ]
```

Setting property values

- You can add your own property values
- The type of the value is preserved, as long as you are within R
- The type of the name (or key) must be `character`

```
mol <- parse.smiles("c1ccccc1Cc2ccccc2")
set.property(mol, "MyProperty", 23.14)
set.property(mol, "toxic", "yes")
get.properties(mol)
```

Persisting molecular data

- You could extract the properties and write them to a text file

```
mols <- load.molecules("data/io/set1.sdf")
props <- lapply(mols, get.properties)

## convert list to table and write it out
props <- do.call("rbind", props)
write.table(props, "drugdata.txt", row.names=FALSE)
```

Persisting molecular data

- Molecular data can also be persisted by writing to SDF format

```
mol <- parse.smiles("c1ccccc1")
set.property(mol, "foo", 1)
set.property(mol, "bar", "baz")
write.molecules(mol, "mol.sdf", write.props=TRUE)
```

Working with molecules

- Currently you can access atoms, bonds, get certain atom properties, 2D/3D coordinates
- Since `rcdk` doesn't cover the entire CDK API, you might need to drop down to the `rJava` level and make calls to the Java code by hand
- I'm happy to code specific tasks in idiomatic R

Working with molecules

- A useful task is to *wash* or *standardize* molecules
- CDK doesn't provide a method to do this directly
- But a common operation is to check for disconnected molecules and keep the largest fragment

```
> m <- parse.smiles("c1ccccc1")
> is.connected(m)
[1] TRUE
>
> m <- parse.smiles("C1CC(N=C1)C(=O)[O-].[Na+]")
> is.connected(m)
[1] FALSE
>
> largest <- get.largest.component(m)
> length(get.atoms(largest))
[1] 8
```

Getting atoms & bonds

- Simple to get atoms and bonds

```
mol <- parse.smiles("c1ccccc1C(Cl)(Br)c1ccccc1")

atoms <- get.atoms(mol)
bonds <- get.bonds(mol)
```

- These are lists of `jobjRef` objects
- `rcdk` currently supports getting the symbol, coordinates, atomic number, implicit H-count
- Can also check whether an atom is aromatic etc.
- `?get.symbol`

Working with atoms

- Simple elemental analysis
- Identifying flat molecules

```
mol <- parse.smiles("c1ccccc1C(Cl)(Br)c1ccccc1")
atoms <- get.atoms(mol)

## elemental analysis
syms <- unlist(lapply(atoms, get.symbol))
round( table(syms)/sum(table(syms)) * 100, 2)

## is the molecule flat?
coords <- do.call("rbind", lapply(atoms, get.point3d))
any(apply(coords, 2, function(x) length(unique(x)) == 1))
```

SMARTS matching

- `rcdk` supports substructure searches with SMARTS or SMILES
- May not be practical for large collections of molecules due to memory

```
mols <- sapply(c("CC(C)(C)C",
                 "c1ccc(Cl)cc1C(=O)O",
                 "CCC(N)(N)CC"), parse.smiles)
query <- "[#6D2]"
hits <- matches(query, mols)

> print(hits)
CC(C)(C)C c1ccc(Cl)cc1C(=O)O CCC(N)(N)CC
FALSE TRUE TRUE
```

Persisting objects

- We already saw how we can persist molecule properties
- It'd be useful to also persist CDK objects (i.e., `jobjRef`'s)

```
m <- parse.smiles("c1ccccc1")

obj <- .jserialize(m)

newObj <- .junserialize(obj)
```

- Serialized objects are just `raw` vectors, so can be saved via `save`
- But also take a look at `.jcache`

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Visualization

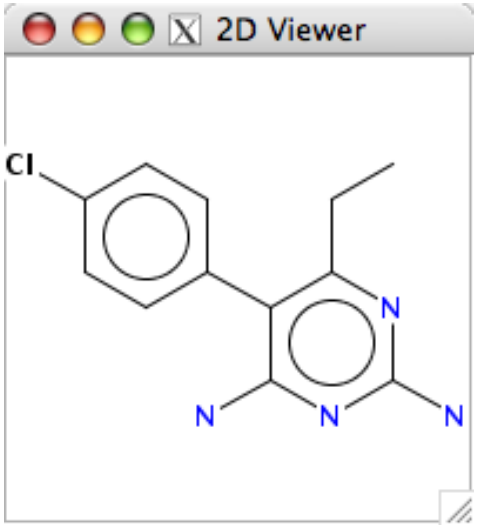
- `rcdk` supports visualization of 2D structure images in two ways
- First, you can bring up a Swing window
- Second, you can obtain the depiction as a raster image
- **Doesn't work on OS X**

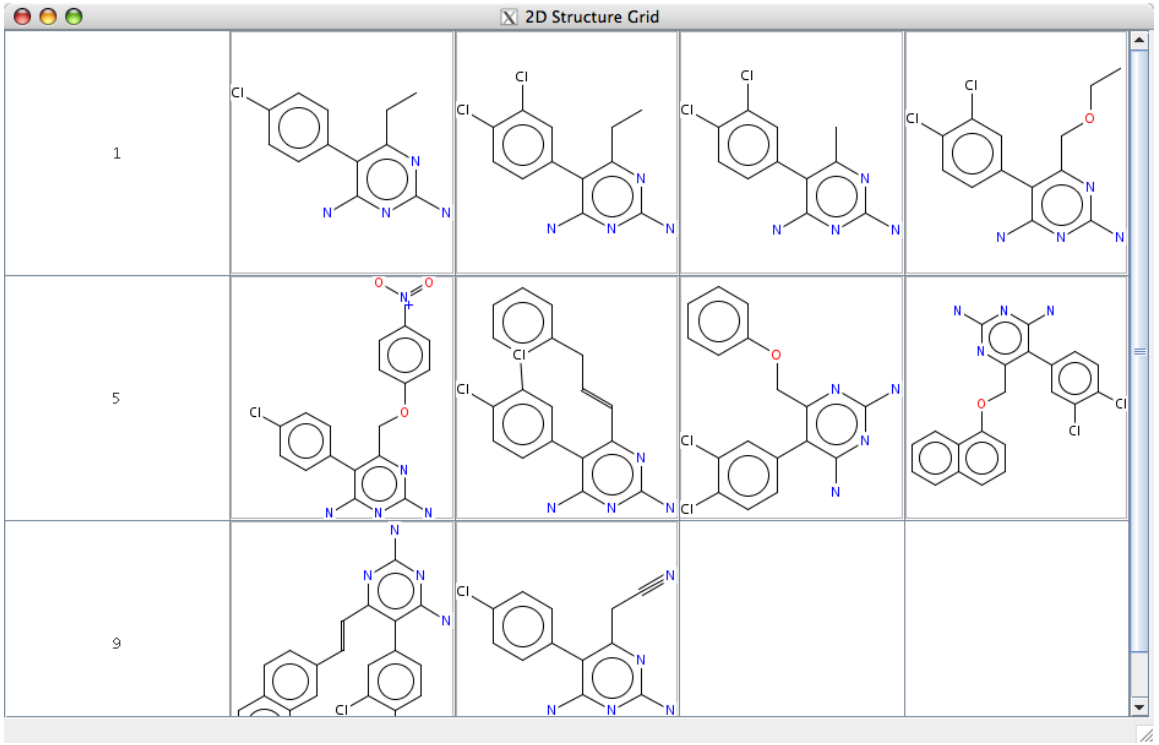
```
mols <- load.molecules("data/dhfr_3d.sd")

## view a single molecule in a Swing window
view.molecule.2d(mols[[1]])

## view a table of molecules
view.molecule.2d(mols[1:10])
```

Visualization





Visualization

- The Swing window is a little heavy weight
- It'd be handy to be able to annotate plots with structures
- Or even just make a panel of images that could be saved to a PNG file
- We can make use of `rasterImage` and `rcdk`
- As with the Swing window, this won't work on OS X

Visualization

```
m <- parse.smiles("c1ccccc1C(=O)NC")
img <- view.image.2d(m, 200,200)

## start a plot
plot(1:10, 1:10, pch=19)

## overlay the structure
rasterImage(img, 1,8, 3,10)
```

Visualization

- By playing around with plotting parameters we can fill up the plot region with an image
- The values being plotted define the coordinates used to overlay the raster image

```
mols <- load.molecules("data/dhfr_3d.sd")

## A table of 16 structures
par(mfrow=c(4,4), mar=c(0,0,0,0))

for (i in 1:16) {
  img <- view.image.2d(mols[[i]], 200, 200)
  plot(1:10, xaxt="n", yaxt="n", xaxs="i", yaxs="i", col="white")
  rasterImage(img, 1,1, 10,10)
}
```

Outline

I/O

Molecular data

Visualization

Descriptors

Fingerprints

Fragments

Molecular descriptors

- Numerical representations of chemical structure features
- Can be based on
  - connectivity
  - 3D coordnates
  - electronic properties
  - combination of the above
- *Many* descriptors are described and implemented in various forms
- The CDK implements 45 descriptor classes, resulting in $\approx$ 300 individual descriptor values for a given molecule

Descriptor caveats

- Not all descriptors are optimized for speed
- Some of the topological descriptors employ graph isomorphism which makes them slow on large molecules
- In general, to ensure that we end up with a rectangular descriptor matrix we do not catch exceptions
- Instead descriptor calculation failures return `NA`

CDK Descriptor Classes

- The CDK provides 3 packages for descriptor calculations
  - `org.openscience.cdk.qsar.descriptors.molecular`
  - `org.openscience.cdk.qsar.descriptors.atomic`
  - `org.openscience.cdk.qsar.descriptors.bond`
- `rcdk` only supports molecular descriptors
- Each descriptor is also described by an ontology
  - For `rcdk` this is used to classify descriptors into groups

Descriptor calculations

- Can evaluate a single descriptor or all available descriptors
- If a descriptor cannot be calculated, `NA` is returned (so no exceptions thrown)
- First need to get available descriptor class names

```
dnames <- get.desc.names()
```

- Gives you a vector of all descriptor class names

Descriptor calculations

- You can also specify descriptor categories, to get a subset

```
dnames <- get.desc.names("topological")

## what categories are available?
> get.desc.categories()
[1] "electronic" "protein" "topological" "geometrical" "constitutional" "h
```

- Depending on the input structures, some descriptors may not make sense
- If you evaluate 3D descriptors from SMILES input, they'd all be set to `NA`

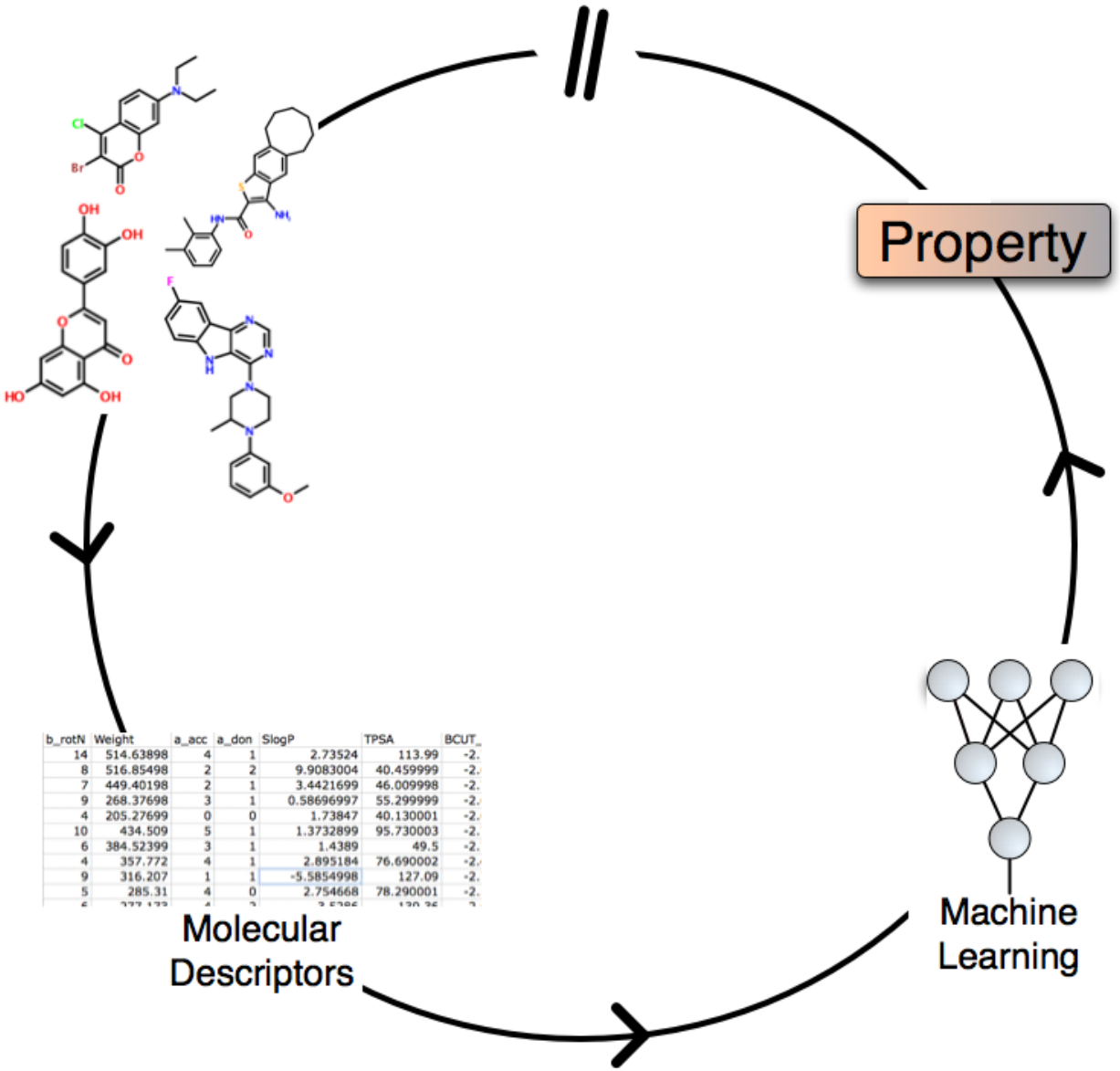
Evaluating the descriptors

- With a set of descriptor class names in hand, you can evaluate them

```
descs <- eval.desc(mols, dnames)
```

- `descs` will be a `data.frame` which can then be used in any of the modeling functions
- Column names are the descriptor names provided by the CDK
- Good practise to put molecule titles in a column or in the row names

The QSAR workflow



b_rotN	Weight	a_acc	a_don	SlogP	TPSA	BCUT_
14	514.63898	4	1	2.73524	113.99	-2.
8	516.85498	2	2	9.9083004	40.459999	-2.
7	449.40198	2	1	3.4421699	46.009998	-2.
9	268.37698	3	1	0.58696997	55.299999	-2.
4	205.27699	0	0	1.73847	40.130001	-2.
10	434.509	5	1	1.3732899	95.730003	-2.
6	384.52399	3	1	1.4389	49.5	-2.
4	357.772	4	1	2.895184	76.690002	-2.
9	316.207	1	1	-5.5854998	127.09	-2.
5	285.31	4	0	2.754668	78.290001	-2.

The QSAR workflow

- Before model development you'll need to clean the molecules, evaluate descriptors, generate subsets
- With the numeric data in hand, we can proceed to modeling
- Before building predictive models, we'd probably explore the dataset
  - Normality of the dependent variable
  - Correlations between descriptors and dependent variable
  - Similarity of subsets
- Then we can go wild and build all the models that R supports

Outline

Accessing fingerprints

- CDK provides several fingerprints
  - Path-based, MACCS, E-State, PubChem
- Access them via `get.fingerprint(...)`
- Works on one molecule at a time, use `lapply` to process a list of molecules
- This method works with the `fingerprint` package
  - Separate package to represent and manipulate fingerprint data from various sources (CDK, BCI, MOE)
  - Uses C to perform similarity calculations
  - Lots of similarity and dissimilarity metrics available

Accessing fingerprints


```
mols <- load.molecules("data/dhfr_3d.sd")

## get a single fingerprint
fp <- get.fingerprint(mols[[1]], type="maccs")

## process a list of molecules
fplist <- lapply(mols, get.fingerprint, type="maccs")
```

- Each fingerprint is an S4 object
- See the `fingerprint` package man pages for more details

Reading fingerprints

- We can also read in fingerprint data generated by other tools - BCI, MOE, CDK

```
fplist <- fp.read("data/fp/fp.data", size=1052,
                  lf=bci.lf, header=TRUE)
```

- Easy to support new line-oriented fingerprint formats by providing your own line parsing function
- See `bci.lf` for an example

Similarity metrics

- The `fingerprint` package implements 28 similarity and dissimilarity metrics
- All accessed via the `distance` function (so you call this even if you want similarity)
- Implemented in C, but still, large similarity matrix calculations are not a good idea!

```
## similarity between 2 individual fingerprints
distance(fplist[[1]], fplist[[2]], method="tanimoto")
distance(fplist[[1]], fplist[[2]], method="mt")

## similarity matrix - compare similarity distributions
m1 <- fp.sim.matrix(fplist, "tanimoto")
m2 <- fp.sim.matrix(fplist, "carbo")

par(mfrow=c(1,2))
hist(m1, xlim=c(0,1))
hist(m2, xlim=c(0,1))
```

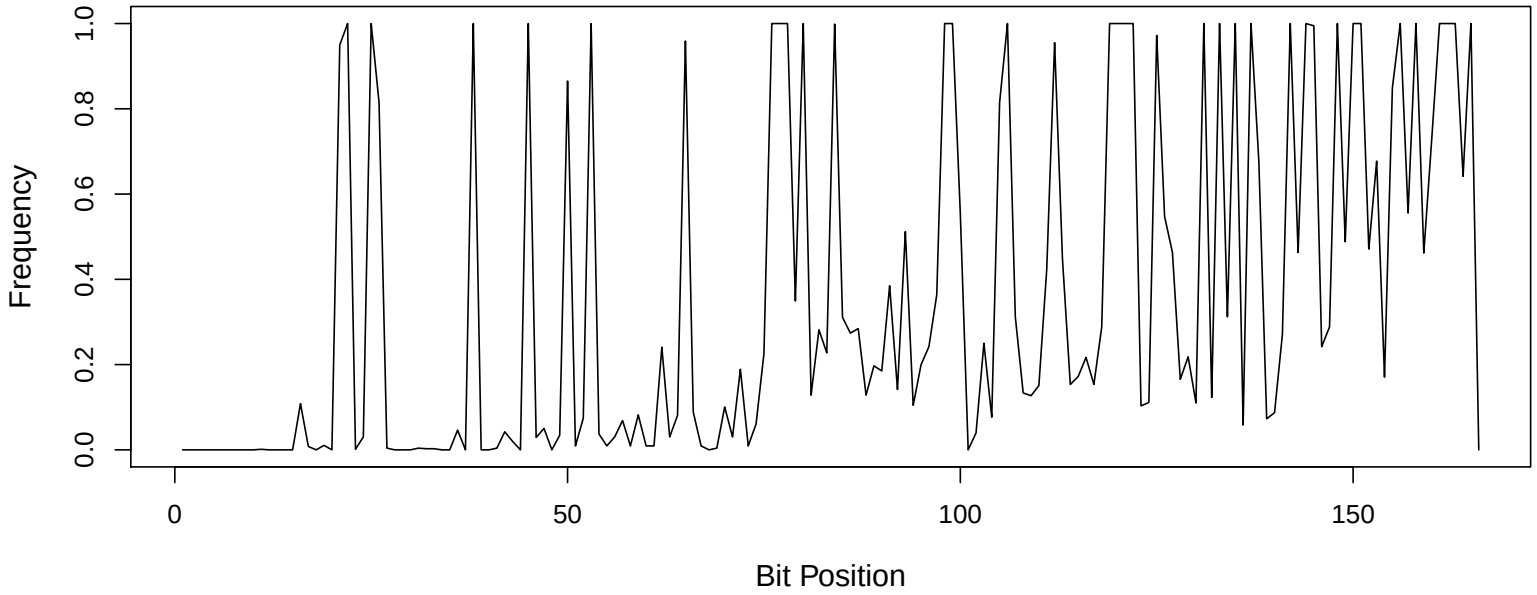
Comparing datasets with fingerprints

- We can compare datasets based on a fingerprints
- Rather than perform pairwise comparisons, we evaluate the normalized occurence of each bit, across the dataset
- Gives us a *n*-D vector - the "bit spectrum"

```
bitspec <- bit.spectrum(fplist)
plot(bitspec, type="l")
```

[0] Guha, R., *J. Comp. Aid. Molec. Des.*, **2008**, *22*, 367–384

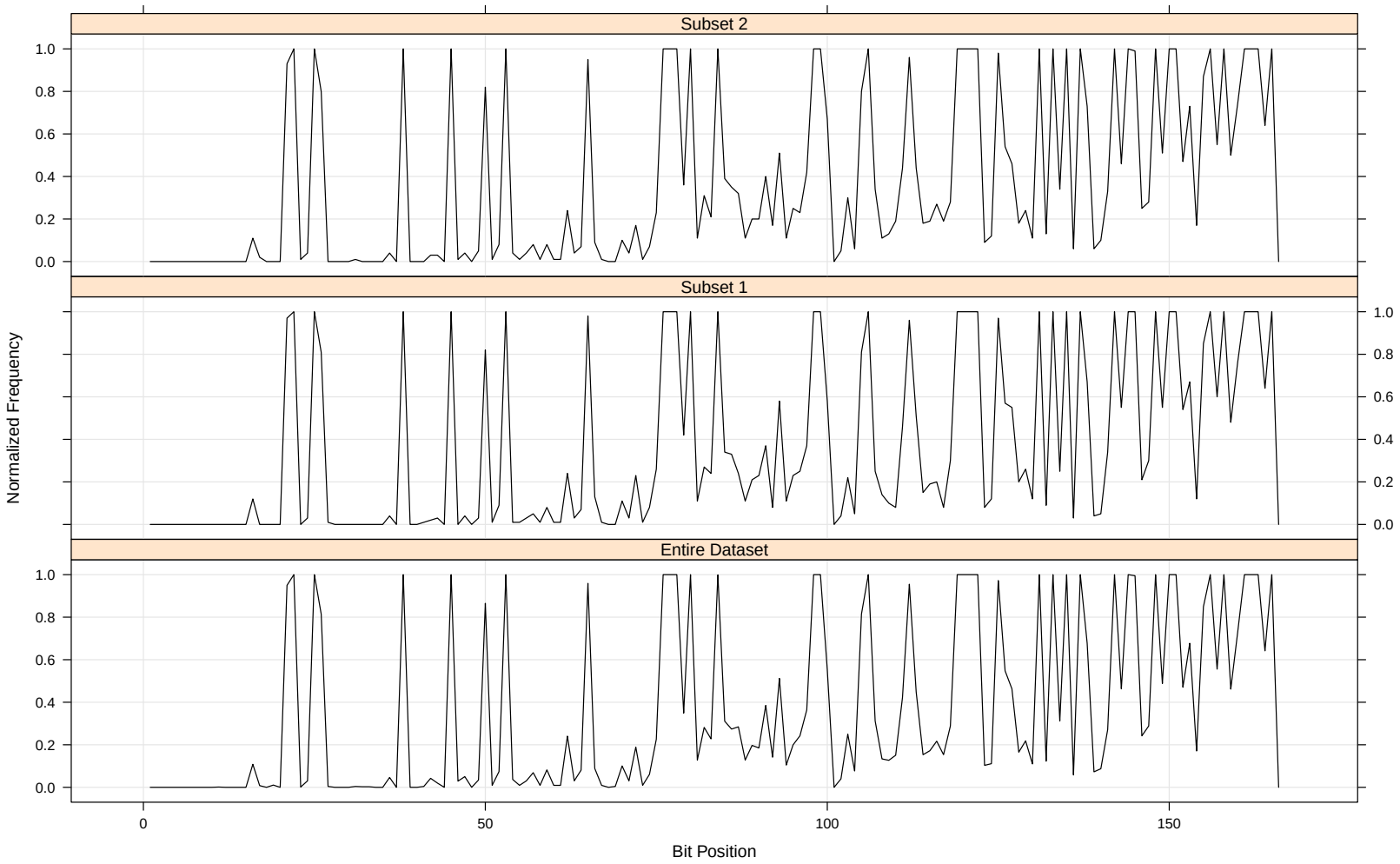
Bit spectrum



- Only makes sense with structural key type fingerprints
- Longer fingerprints give better resolution
- Comparing bit spectra, via any distance metric, allows us to compare datasets in $O(n)$ time, rather than $O(n^2)$ for a pairwise approach

[0] Guha, R., *J. Comp. Aid. Molec. Des.*, **2008**, *22*, 367–384

Comparing datasets



Fingerprints & clustering

- Clustering large collections is not practical
- Any way to avoid a pairwise similarity matrix is desirable

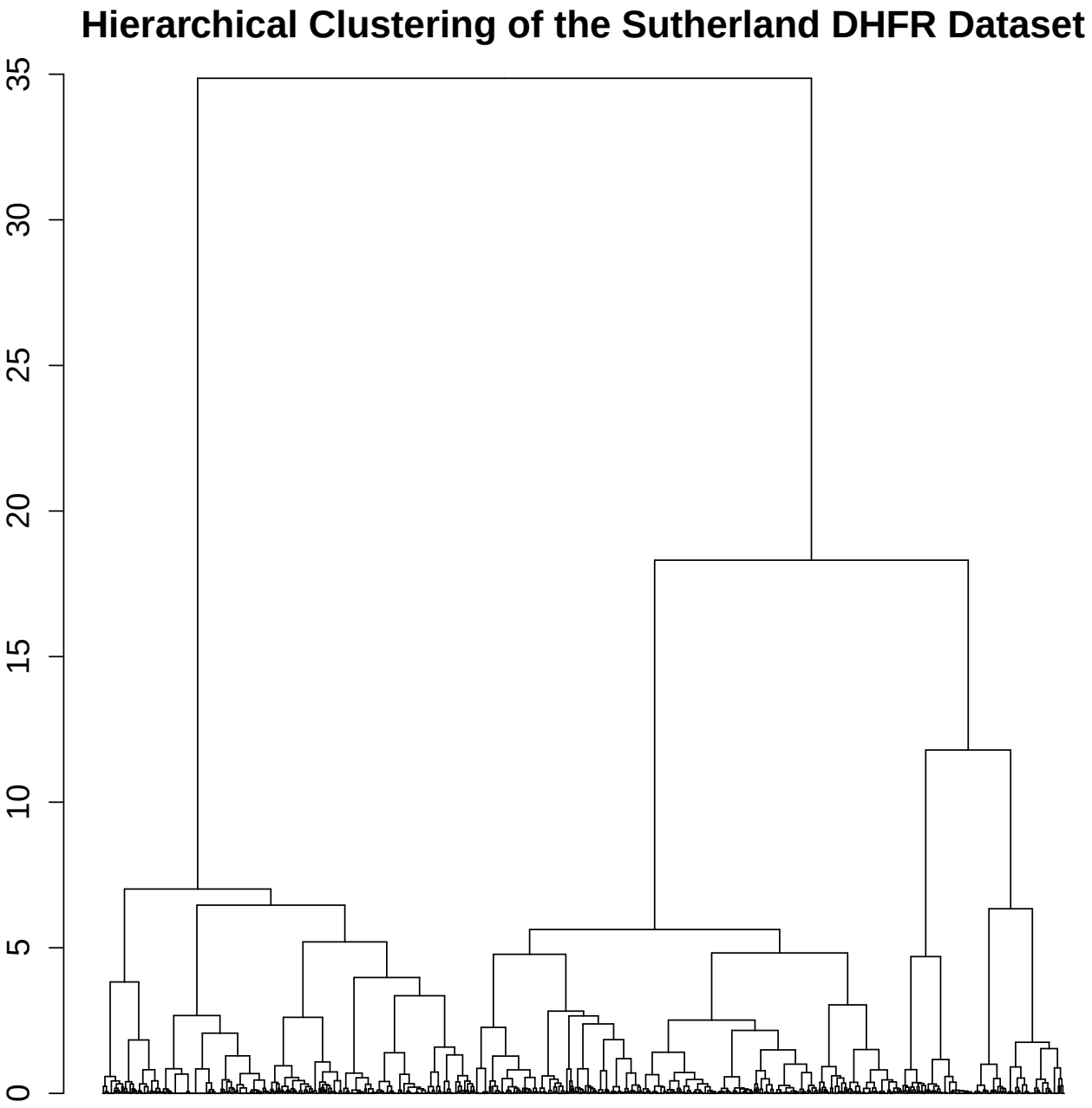
```
## Get fingerprints
mols <- load.molecules("data/dhfr_3d.sd")
fplist <- lapply(mols, get.fingerprint, type="maccs")

## Gives us a similarity matrix
fpdist <- fp.sim.matrix(fplist)

## Convert to a distance matrix
fpdist <- as.dist(1-fpdist)

## Perform the clustering
clus <- hclust(fpdist, method="ward")
```

Fingerprints & clustering

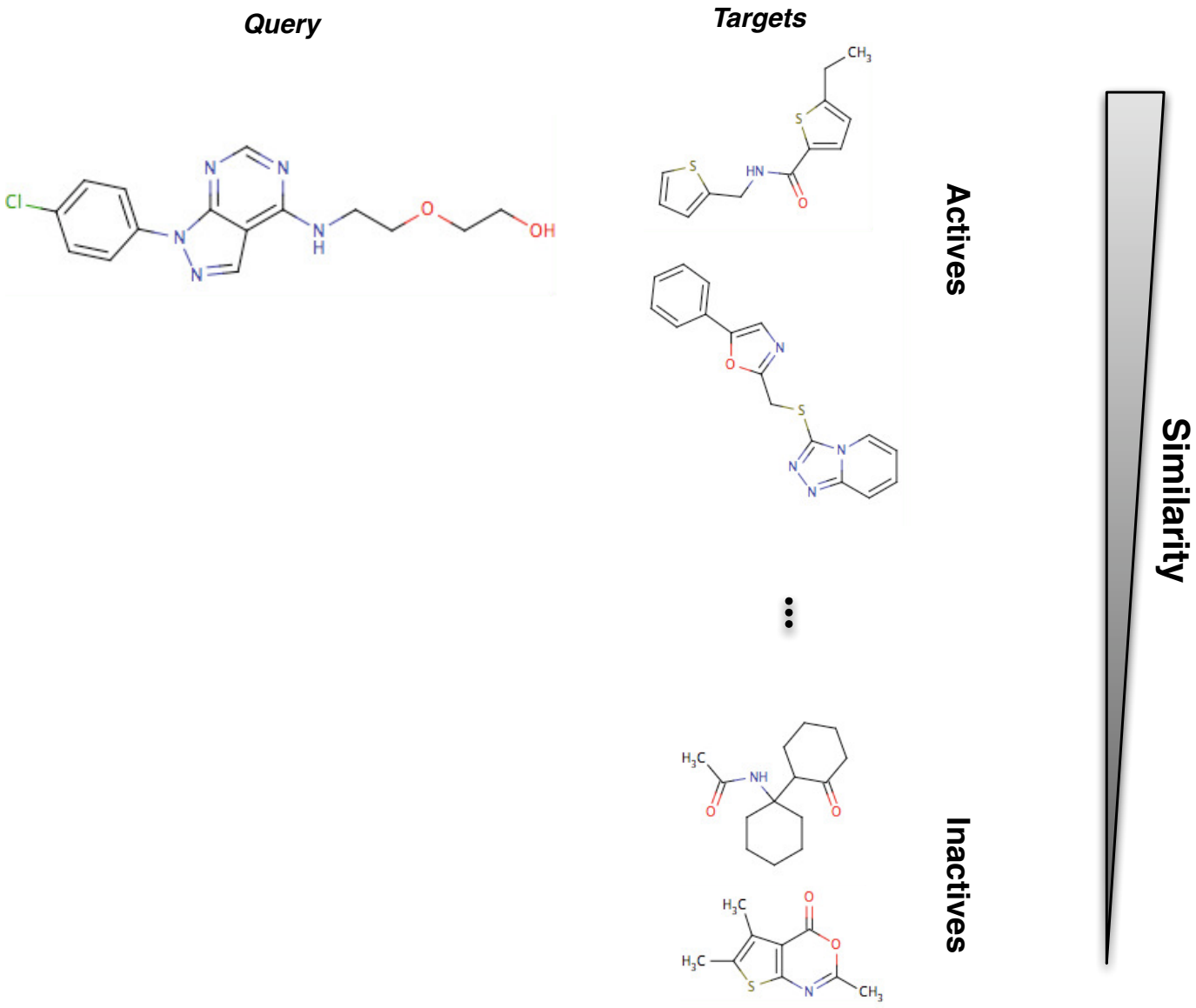


Comparing fingerprint performance

- Various studies comparing virtual screening methods
- Generally, metric of success is how many actives are retrieved in the top $n\%$ of the database
- Can be measured using ROC, enrichment factor, etc.
- Exercise - evaluate performance of CDK fingerprints using enrichment factors
  - Load active and decoy molecules
  - Evaluate fingerprints
  - For each active, evaluate similarity to all other molecules (active and inactive)
  - For each active, determine enrichment at a given percentage of the database screened

For a given query molecule, order dataset by decreasing similarity, look at the top 10% and determine fraction of actives in that top 10%

Comparing fingerprint performance

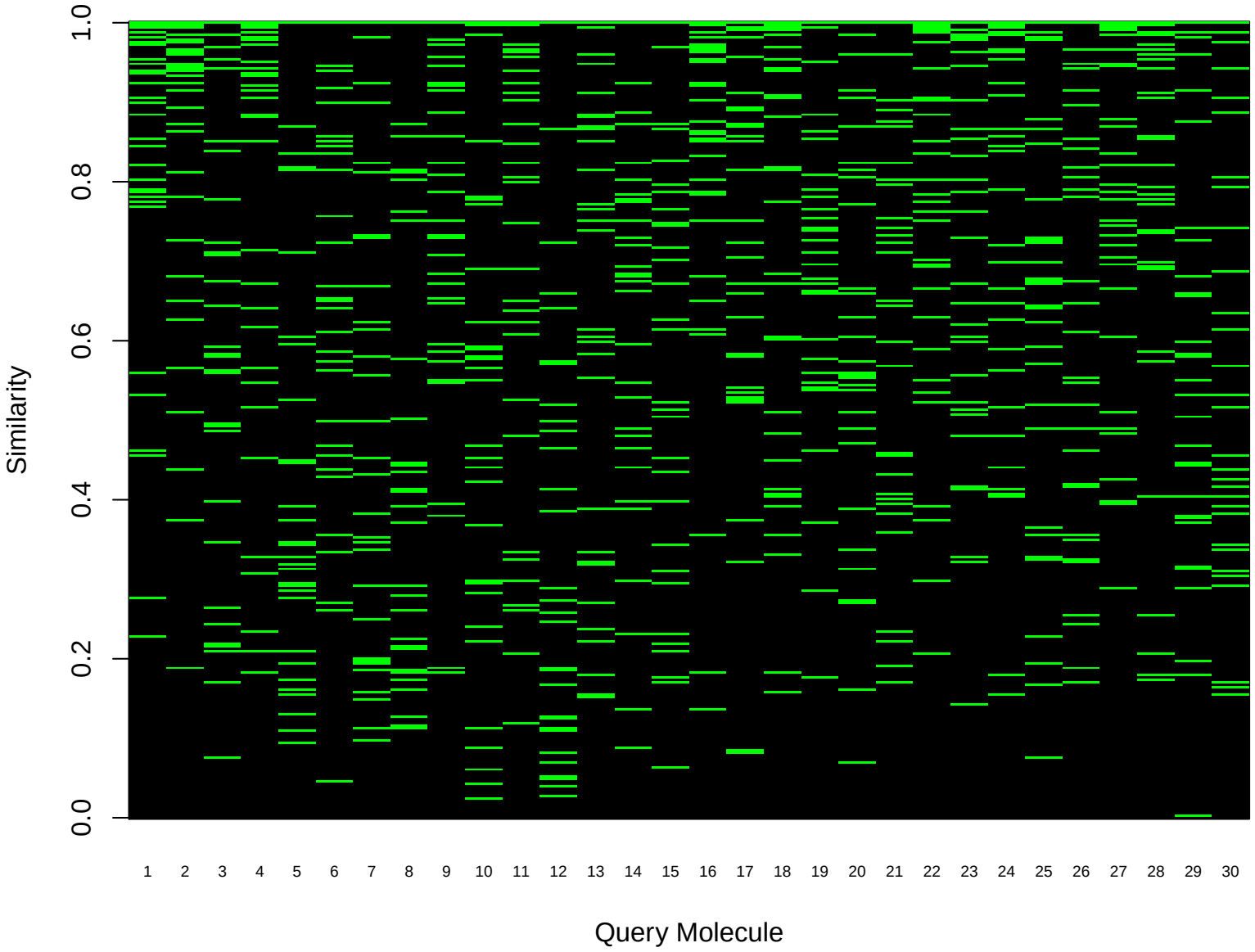


Comparing fingerprint performance

- A good dataset to test this out is the Maximum Unbiased Validation datasets by Rohr & Baumann
- Derived from 17 PubChem bioassay datasets and designed to avoid *analog bias* and *artifical enrichment*
- As a result, 2D fingerprints generally show poor performance on these datasets (by design)
- See here for a comparison of various fingerprints using two of these datasets

[0]Rohrer, S.G et al, *J. Chem. Inf. Model*, **2009**, *49*, 169–184
[0]Good, A. & Oprea, T., *J. Chem. Inf. Model*, **2008**, *22*, 169–178
[0]Verdonk, M.L. et al, *J. Chem. Inf. Model*, **2004**, *44*, 793–806

Comparing fingerprint performance



Outline

Fragment based analysis

- Fragment based analysis can be a useful alternative to clustering, especially for large datasets
- Useful for identifying interesting series
- Many fragmentation schemes are available
  - Exhaustive
  - Rings and ring assemblies
  - Murcko
- The CDK supports fragmentation (still needs work) into Murcko frameworks and ring systems
- We can also use the NCGC fragmenter (see `data/fragmenter.jar`) to exhaustively generate fragments

Getting fragments

- `rcdk` currently wraps the `GenerateFragments` class
- Only exposes the Murcko fragmentation method
- Lets look at directly working a CDK class and its methods
- Once we have the fragmenter we can perform a Murcko fragmentation and get back the fragments as SMILES

Getting fragments

```
mol <- parse.smiles(
"c1cc(c(cc1c2c(nc(nc2CC)N)N)[N+](=O)[O-])NCc3ccc(cc3)C(=O)N4CCCCC4")

## get the fragmenter
fragmenter <- .jnew("org/openscience/cdk/tools/GenerateFragments")

## do fragmentation
.jcall(fragmenter, "V", "generateMurckoFragments",
      .jcast(mol, "org/openscience/cdk/interfaces/IMolecule"),
      TRUE, TRUE, as.integer(6))

## get fragments as SMILES
frags <- .jcall(fragmenter,
              "[S",
              "getMurckoFrameworksAsSmileArray")
```

Some caveats

- The fragment SMILES come out as non-aromatic
- There is supposed to be a way to get the appropriate SMILES out, currently looking into this
- Implies that if we want to look at *fragment properties*, we're stuck
- However, we can still use these to look at series and/or local trends etc.

Aggregating fragments

- Lets wrap the fragmentation procedure into a function

```
get.frags <- function(mol, fragmenter) {
  .jcall(fragmenter, "V", "generateMurckoFragments",
         .jcast(mol, "org/openscience/cdk/interfaces/IMolecule"),
         TRUE, TRUE, as.integer(6))
  return(.jcall(fragmenter, "[S", "getMurckoFrameworksAsSmileArray"))
}
```

Aggregating fragments

- Now, we can get fragments for a set of molecules

```
mols <- load.molecules("data/dfhr_3d.sd")
fragmenter <- .jnew("org/openscience/cdk/tools/GenerateFragments")
frags <- lapply(mols, function(x, f) {
    get.frags(x, f)
}, f=fragmenter)
```

Aggregating fragments

- This gives us a list of fragment SMILES

```
> frags[1:3]
[[1]]
[1] "C1=CC=C(C=C1)C=2C=NC=NC=2"

[[2]]
[1] "C1=CC=C(C=C1)C=2C=NC=NC=2"

[[3]]
[1] "C1=CC=C(C=C1)C=2C=NC=NC=2"
```

- What we want is a `data.frame` that associates fragments, fragment ID's and the SMILES from which they are derived

Aggregating fragments

```
frags <- lapply(mols, function(x, f) {
  tmp <- get.frags(x, f)
  tmp <- data.frame(frag=I(tmp),
                    mol=I(get.property(x, "cdk:Title")))
  return(tmp)
}, f=fragmenter)
frags <- do.call("rbind", frags)
```

- Now we have something useful to work with

```
> head(frags)
                          frag mol
1 C1=CC=C(C=C1)C=2C=NC=NC=2 1-pyrimethamine
2 C1=CC=C(C=C1)C=2C=NC=NC=2 1-3062
3 C1=CC=C(C=C1)C=2C=NC=NC=2 1-7364
4 C1=CC=C(C=C1)C=2C=NC=NC=2 1-115194
5 C1=CC=C(C=C1)OCC=2C=CN=CN=2 1-118203
6 C1=CC=C(C=C1)C=2C=NC=NC=2 1-118203
```

Aggregating fragments

- Finally we generate some arbitrary fragment ID's

```
ufrags <- data.frame(frag=I(unique(frags$frag)),
                     fid=I(sprintf("F%03d")),
                         1:length(unique(frags$frag)))))
frags <- merge(frags, ufrags, by="frag")
```

- ... giving us

```
> tail(frags)
                                        frag mol fid
963 O=C2NC=NC=3NC=C(CNC1=CC=CC=C1)C2=3 43-13 F239
964 O=C2NC4=NC=NC=C4(C=3CN(CC1=CC=CC=C1)CC2=3) 49-4 F265
965 O=S(=O)(C1=CC=CC=C1)C=2C=CC3=NC=NC=C3(N=2) 22-8 F150
966 O=S(=O)(C1=CC=CC=C1)C=2C=CC3=NC=NC=C3(N=2) 22-9 F150
967 O=S(=O)(C1=CC=CC=C1)C=2C=CC3=NC=NC=C3(N=2) 22-7 F150
968 O=S(=O)(NCCOC1=CC=CC=C1)C2=CC=CC=C2 1-122059 F068
```

Doing stuff with fragments

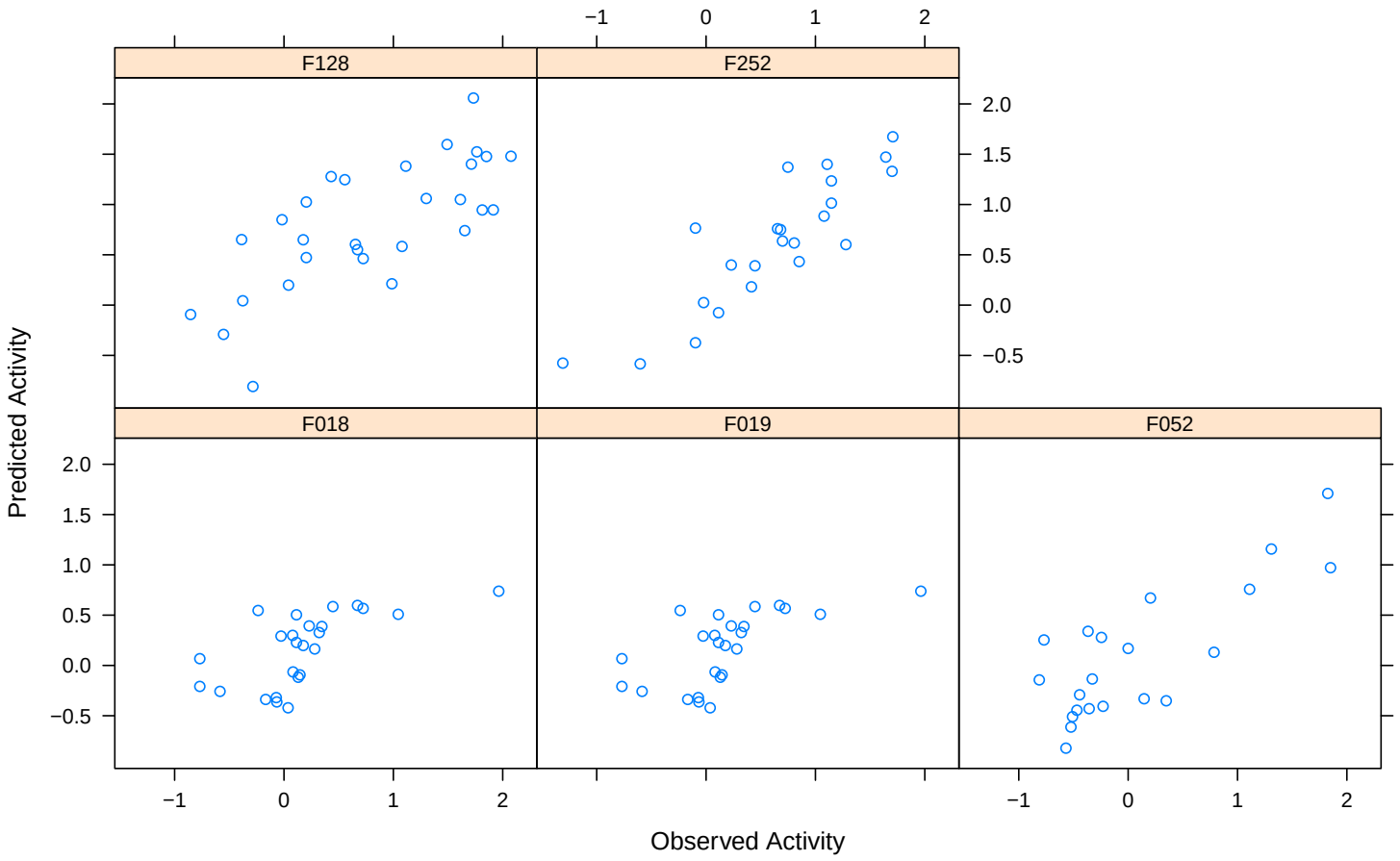
- Look at frequency of occurence of fragments
- Develop predictive models on fragment members, looking for local SAR
- *Pseudo-cluster* a dataset based on fragments
- Compound selection based on fragment membership

```
frag.counts <- by(frags, frags$frag, nrow)
barplot(frag.counts)
```

Characterizing fragment SAR

- Consider some of the larger series and see if there is an SAR within each of them
- Strategy
  - Identify fragments with 20 to 30 members
  - Merge the fragment data with descriptor data for the associated molecules
  - For each fragment series, build an OLS model using exhaustive feature selection
- I've precalculated a set of descriptors for this purpose (`d` in `data/frags.Rda`) or you can generate fragments yourself

Characterizing fragment SAR

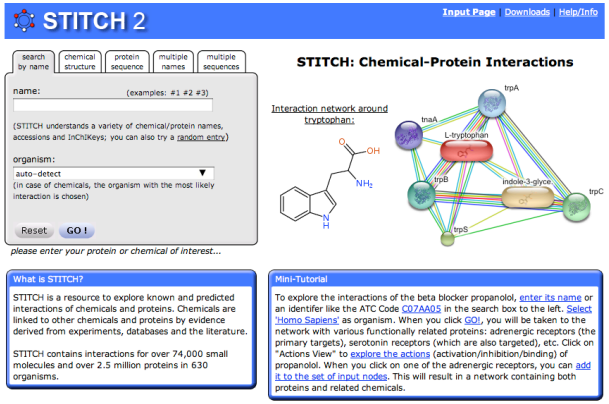


Predicted versus observed activity for 5 fragment series, based on OLS models and exhaustive feature selection

Part IV

Cheminformatics & R - `rpubchem`

Public chemical and biological data



DrugBank

ChemSpider
Building community for chemists

PubChem

eMolecules
Searching the World's Chemistry

ChEBI

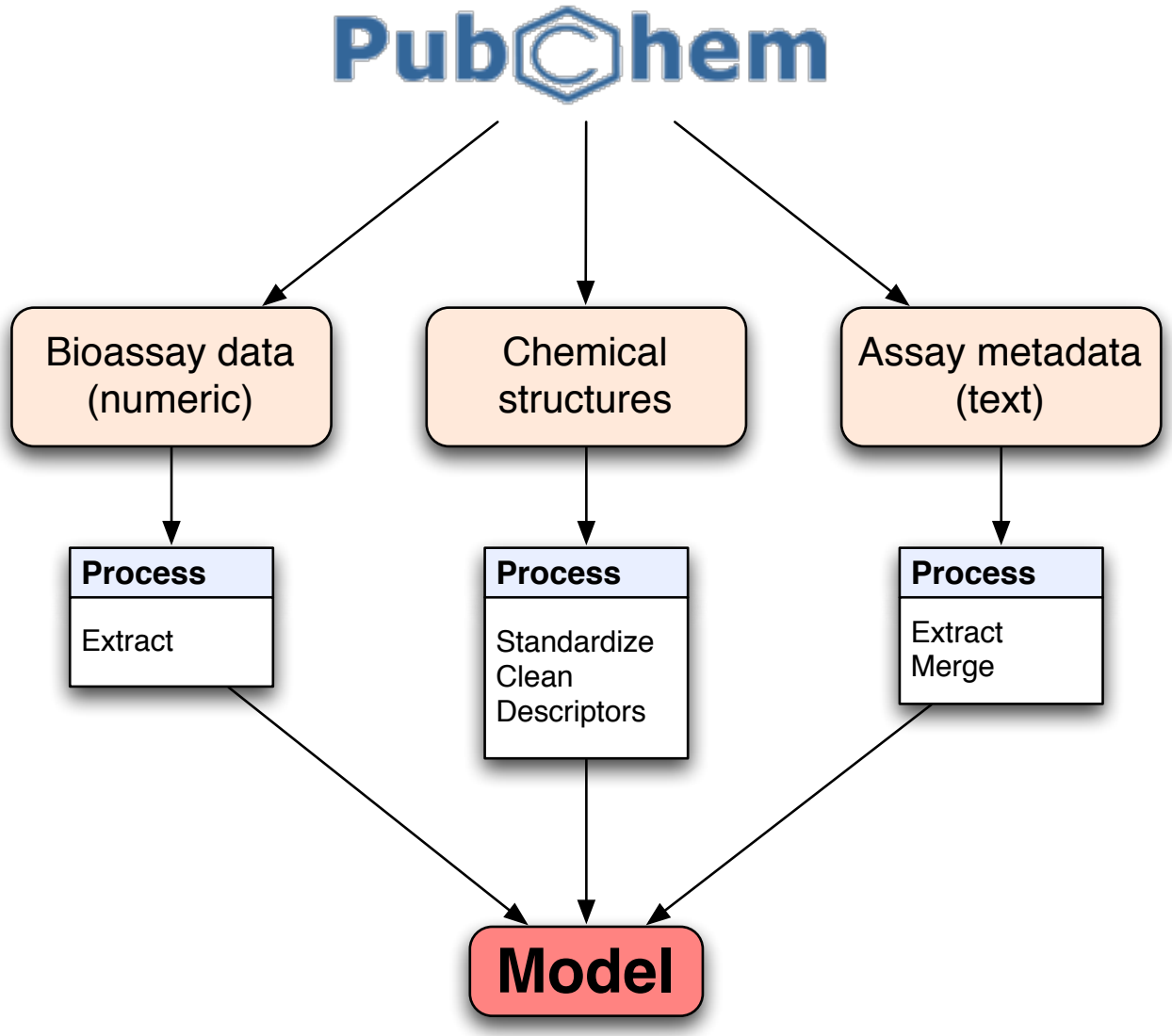
ChemBank

PDSP
K_i Database

BindingDB

chEMBL

Working with PubChem data



Working with PubChem data in R

- Access PubChem datasets using idiomatic R
- Minimize extra work (merge data, add metadata etc)
- End up with a `data.frame`, ready for modeling
- The usual sequence of tasks would involve
  - Get the assay data
  - Get structure data associated with the assay
  - Proceed with modeling

Working with PubChem data in R

- Access PubChem datasets using idiomatic R
- Minimize extra work (merge data, add metadata etc)
- End up with a `data.frame`, ready for modeling
- The usual sequence of tasks would involve
  - Get the assay data
  - Get structure data associated with the assay
  - Proceed with modeling

Getting assay data

- The workhorse method is `get.assay` which takes the AID as argument

```
assay <- get.assay(2018, quiet=FALSE)
```

- Returns a `data.frame` derived from the assay data CSV file and the assay description XML file form PubChem
- The *description*, *comments* and field descriptions and types are available as attributes of the `data.frame`
- **Note** - no structures are included at this point

Other ways to get assay data

- If you're looking for a group of assays, say related to HDAC inhibitors, perform a keyword search

```
## gives a vector of integer AIDs
aids <- find.assay.id("HDAC", quiet=FALSE)

## what are the assays?
sapply(aids[1:10], get.assay.desc)
```

Other ways to get assay data

- Find assays that a compound is active in

```
cid <- 68368
aids <- get.aid.by.cid(cid, type="active")
```

- Gives a vector AIDs that the compound is active in
- If you specify `type="raw"`, a summary is returned

Getting structure information

- Get structure data by CID or SID

```
cids <- get.cid(assay$PUBCHEM.CID[1:10])
```

- Gives you a `data.frame` containing name, structure and some properties

```
> str(structs)
'data.frame': 10 obs. of 11 variables:
 $ CID : chr "644436" "645300" "645983" "648874" ...
 $ IUPACName : chr "2-(2-methylphenyl)-1,3-benzoxazol-5-amine"
 $ CanonicalSmile : chr "CC1=CC=CC=C1C2=NC3=C(O2)C=CC(=C3)N"
 $ MolecularFormula : chr "C14H12N2O" "C18H15N3O2" "C24H34N6O3"
 $ MolecularWeight : num 224 305 455 407 290 ...
 $ TotalFormalCharge : int 0 0 0 0 0 0 0 0 0 0
 $ XLogP : num 3.1 3.2 3 4.5 2.1 2.9 1.8 2.5 0.7 1.7
 $ HydrogenBondDonorCount : int 1 0 1 1 2 2 1 1 2 2
 $ HydrogenBondAcceptorCount: int 3 4 7 5 4 3 7 8 5 4
 $ HeavyAtomCount : int 17 23 33 29 21 26 33 31 20 21
 $ TPSA : num 52 57 94.4 68 84.5 70.7 94.4 125 104 69.6
```

Ready to model

- Having gotten the `data.frame` of structures we can parse the SMILES into CDK objects and evaluate descriptors
- However, `get.cid` (and `get.sid`) will not work if you try and retrieve too many at one go
- The current design makes an Entrez URL, which can become too large and so is rejected
- Will be switching to the use of PUG
- In the meantime, retreive structure data in chunks

Getting CID data in chunks


```
## will likely fail
structs <- get.cid(assay$PUBCHEM.CID)

## better way, 300 CIDs at a time
library(itertools)
chunks <- as.list(ichunk(assay$PUBCHEM.CID, 300))
structs <- lapply(chunks, get.cid)
structs <- do.call("rbind", structs)
```

Part V

Extending `rcdk`

Why extend?

- `rcdk` doesn't cover the whole CDK API
- I add functions as and when I need them (or if someone asks)
- If you want to access CDK classes and methods, you can use `rJava` (such as `.jnew` and `.jcall`)
  - This can get a bit cumbersome
  - Use the soure code for inspiration
- For more complex stuff, you can write Java code that gets installed along with `rcdk`
  - Ideally this would get contributed back and incorporated into the `rcdk.jar` file that is bundled with the `rcdk` package

Structure of the `rcdk` package

Name	Date Modified	Size	Kind
data	May 7, 2010, 2:31 PM	--	Folder
rcdk	Today, 3:55 PM	--	Folder
data	May 3, 2010, 10:33 AM	--	Folder
DESCRIPTION	Today, 9:41 AM	4 KB	Plain text
inst	May 3, 2010, 10:33 AM	--	Folder
CITATION	May 3, 2010, 10:33 AM	4 KB	Plain text
cont	May 6, 2010, 8:24 AM	--	Folder
doc	Today, 2:47 PM	--	Folder
unitTests	Today, 9:41 AM	--	Folder
man	Today, 9:41 AM	--	Folder
NEWS	May 3, 2010, 10:33 AM	4 KB	Plain text
R	Today, 9:41 AM	--	Folder
tests	May 3, 2010, 10:33 AM	--	Folder
doRUnit.R	May 3, 2010, 10:33 AM	4 KB	R Code File

- If you add new functionality, good idea to add unit tests (using `RUnit`) under `rcdk/inst/unitTests/`

Structure of the cdkr project

Name	Date Modified	Size	Kind
data	May 7, 2010, 2:31 PM	--	Folder
rcdk	Today, 9:41 AM	--	Folder
data	May 3, 2010, 10:33 AM	--	Folder
DESCRIPTION	Today, 9:41 AM	4 KB	Plain text
inst	May 3, 2010, 10:33 AM	--	Folder
man	Today, 9:41 AM	--	Folder
NEWS	May 3, 2010, 10:33 AM	4 KB	Plain text
R	Today, 9:41 AM	--	Folder
tests	May 3, 2010, 10:33 AM	--	Folder
rcdkjar	Today, 3:49 PM	--	Folder
build.properties	May 3, 2010, 10:33 AM	Zero KB	Document
build.xml	May 3, 2010, 10:33 AM	4 KB	Text ...ument
jars	May 6, 2010, 8:24 AM	--	Folder
rcdk.iml	May 6, 2010, 8:24 AM	4 KB	Document
rcdk.ipr	May 6, 2010, 8:24 AM	20 KB	IntelliJ...ct File
rcdk.iws	May 6, 2010, 8:24 AM	40 KB	Document
src	May 3, 2010, 10:33 AM	--	Folder
rcdklibs	May 6, 2010, 8:24 AM	--	Folder
README.md	May 6, 2010, 8:24 AM	4 KB	Document

- Within `rcdkjar/`, run `ant jar` to build the jar file and copy into the `rcdk` package directory
- Generally, no need to touch `rcdklibs/`

Writing Java in R

- Don't like it, but sometimes it's easier than firing up the Java IDE. Need to be familiar with the CDK API
- Three main functions
  - `.jnew`
  - `.jcall`
  - `.jcast`

Writing Java in R

- First, lets look at a better way to get the atom count of a molecule
- Right now, we get a molecule and get the list of atom objects and return the length of the list
- But `IAtomContainer` has a method `getAtomCount()`

```
m <- parse.smiles("CCC")
.jcall(mol, "I", "getAtomCount")
```

- For static methods, the first cargument can be the fully qualified class name
- You do need to specify the return type in JNI notation

Writing Java in R

JNI Signature	Java Type
I	int
Z	boolean
B	byte
C	char
L*fully-qualified-class*;	fully-qualified-class
[*type*	*type*[]

- For the *L* signature, remember the semi-colon at the end

Writing Java in R

- Another example is getting the largest connected component
- We make use of the `ConnectivityChecker` class and the `partitionIntoMolecules` method

```
mol <- parse.smiles("CCC(=O)C[O-].[Na+]")
molSet <- .jcall("org.openscience.cdk.graph.ConnectivityChecker",
                 "Lorg/openscience/cdk/interfaces/IMoleculeSet;",
                 "partitionIntoMolecules", mol)
ncomp <- .jcall(molSet, "I", "getMoleculeCount")
```

Writing Java in Java

- When writing Java in R gets too tedious, switch to Java in Java
- You could write classes to do the work and then package them into a jar
- Copy the jar into the `inst/cont` of the `rcdk` directory
- Edit `.First.lib` in `R/rcdk.R` to add this jar to the classpath
- Alternatively edit the Java sources for the `rcdk` package
  - Need to access the Github repository

Future developments

- Update `rpubchem` to use PUG throughout
- Data table and depictions
- Streamline I/O and molecule configuration
- Add more atom and bond level operations
- Convert from `jobjRef` to S4 objects and vice versa
  - Would allow for serialization of CDK data classes
  - Is it worth the effort?
- Your suggestions